Ulnar Neuropathy at Elbow (U.N.E) in people with haemophilia, attending a multispecialty clinic in a tertiary care centre in South India: An Observational Study.

Dissertation submitted to the Tamil Nadu Dr.MGR Medical University, Chennai,

in partial fulfillment of the requirements for the

MD Branch XIX (Physical Medicine and Rehabilitation) examination in March 2013

CERTIFICATE

This is to certify that "Ulnar Neuropathy at Elbow (U.N.E) in people with haemophilia, attending a Multi specialty clinic in a tertiary care centre in South India: An observational study." is the bona fide work of Dr Prashanth H Chalageri, Candidate number 20116503, in partial fulfillment of the requirement of The Tamil Nadu Dr MGR Medical University, Chennai, for the MD Branch XIX (Physical Medicine and Rehabilitation) examination in March 2013.

Dr. Alfred Job Daniel

Principal

Christian Medical College

Vellore

Certificate

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Dr Raji Thomas

Professor,

Department of Physical Medicine and Rehabilitation.

Christian Medical College

Vellore

Acknowledgement:

I express my deep gratitude to Dr Raji Thomas for initiating and guiding me throughout the study, Dr Judy Ann John for teaching me the clinical approach to haemophilia, Dr Apurba Barman, Dr Rohit Bhide, Dr Ahana Chatterjee, Dr Anand V who taught me the nuances of electrophysiology and to Dr George Tharion, Dr Suranjan Bhattacharjee and Dr Jacob George for their constant encouragement. I would like to thank all the team members who are a part of the "Haemophilia Clinic" who are constantly striving to help the patients with haemophilia. A big thanks to all my colleagues who helped me in completing this dissertation by helping in finding articles and with the clinical work while I was busy writing this dissertation. Thanks to Dr Prasanna, who helped me with the statistical analysis of the results.

The credit for this study truly goes to all the patients with haemophilia who agreed to take time to participate in the study and their caregivers who waited patiently during the nerve conduction studies .This study is my humble effort in working towards a better quality of life for all the patients with haemophilia.

Dr Prashanth H Chalageri

:

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ABSTRACT OF DISSERTATION

TITLE OF THE ABSTRACT: Ulnar Neuropathy at Elbow (U.N.E) in people with haemophilia,attending a Multispecialty clinic in a tertiary care centre in SouthIndia: An Observational Study.

DEPARTMENT: Physical Medicine and Rehabilitaion.

NAME OF THE CANDIDATE: Dr Prashanth H Chalageri

DEGREE AND SUBJECT: MD in Physical Medicine and Rehabilitation

NAME OF THE GUIDE: Dr Raji Thomas

OBJECTIVES: To find the point prevalence of UNE in hemophilia patients attending a multi-disciplinary clinic in a tertiary care centre in South India and its correlation with various parametres.

METHODS: 50 patients satisfying the inclusion and exclusion criteria were included in the study. History reagrding their disease severity, frequency of joint bleeds, symptoms of UNE were taken. All were examined clinically and electrophysiologically for signs of UNE. UNE was diagnosed based on criteria by AAEM. Elbow Xrays taken as a part of treatment, were analysed for joint involvement. Descriptive statistics - mean, standard deviation and range were done for continuous data. Univariate analysis of the variables from data and their association with UNE was done by using ChiSquare test and Chi Squre for trend test.

RESULTS: The prevalence of UNE in haemophilia patients attending our hospital was 42/100haemophilia patients. There was no association between stage of haemophilic arthropathy andUNE (OR<1, p value <0.05). Statistically significant association (p value<0.05) was found between UNEand Elbow joint being a target joint (OR 3.69) and between X ray involvement of ulnohumeral joint (OR 1.36) and UNE.

INSTITUTIONAL REVIEW BOARD (IRB)
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VELLORE 632 002, INDIA

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Additional Vice Principal(Research)

October 12, 2011

Dr. Prashanth H Chalageri
PG Registrar
Department of PMR
Christian Medical College
Vellore 632 002

Sub: **FLUID Research grant project NEW PROPOSAL**:
Ulnar Neuropathy at Elbow (U.N.E) in people with hemophilia attending multispecialty clinic in a tertiary care centre in South India: An observational study
Dr. Prashanth H Chalageri, PG Registrar, PMR, Dr. Raji Thomas, Dr. Judy Ann John, Dr. Apurba Barman, PMR

Ref: IRB Min. No. 7630 dated 3.10.2011

Dear Dr. Chalageri,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Ulnar Neuropathy at Elbow (U.N.E) in people with hemophilia attending multispecialty clinic in a tertiary care centre in South India: An observational study" on October 3, 2011.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Informed Consent Form and Information Sheet (English, Tamil and Hindi)
3. Questionnaire
4. Cvs of Drs. Prashanth H Chalageri, Raji Thomas, Judy Ann John, Dr. Apurba Barman.
5. A CD containing documents 1 3

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE
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Secretary, Research Committee, IRB
Additional Vice Principal(Research)

The following Institutional Review Board (Ethics Committee) members were present at the meeting held on October 3, 2011 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore- 632002.

Name	Qualification	Designation	Other Affiliations
Dr. B.J.Prashantham	MA (Counseling), MA (Theology), Dr Min(Clinical)	Chairperson(IRB)& Director, Christian Counselling Centre	Non-CMC
Mr. Harikrishnan	BL	Lawyer	Non-CMC
Mrs. Mary Johnson (on behalf of Dr. Jayarani Premkumar)	M.Sc. (Nursing), Ph.D.	Nursing Superintendent, CMC.	
Dr. Vadhesala Sadan (on behalf of Mrs. Rosaline Jayakaran)	M.Sc. (Nursing), RN, RM	Dean, College of Nursing, CMC.	
Dr. Gagandeep Kang	MD, PhD, FRCPath.	Secretary IRB (EC)& Dy. Chairperson (IRB), Professor of Microbiology & Addl. Vice Principal (Rese CMC.	

We approve the project to be conducted as presented.

The Institutional Ethics Committee / Independent Ethics Committee expects to be informed about the progress of the project, any SAE occurring in the course of the project, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

A sum of ₹ 27,000/- (Rupees Twenty seven thousand only) is sanctioned for 1 year.

Yours sincerely,

Dr. Alfred Job Daniel
Principal & Chairperson (Research Committee)
Institutional Review Board

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

Turnitin Originality Report

Ulnar Neuropathy at Elbow (U.N.E) in people with haemophilia attending a multi specialty clinic in a tertiary care centre in South India: An observational study by Prashanth H. Chalageri 20116503

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Ulnar Neuropathy at Elbow (U.N.E) in people with haemophilia attending a multispecialty clinic in a tertiary care centre in South India: An Observational Study.

PLACE OF STUDY

Department of Physical Medicine and Rehabilitation

Christian Medical College

Vellore, Tamil Nadu

Ulnar Neuropathy at Elbow (U.N.E) in people with haemophilia, attending a multispecialty clinic in a tertiary care centre in South India: An Observational Study.

Aim:

To study the prevalence of Ulnar Neuropathy at Elbow (UNE) in people with hemophilia.

OBJECTIVES:

A. To find the point prevalence of UNE in hemophilia patients attending a multi-disciplinary clinic in a tertiary care centre in South India through history, clinical examination and nerve conduction velocity studies.

B. To study the correlation of ulnar neuropathy at elbow in people with hemophilia with frequency of elbow bleeds, stage of haemophilic arthropathy of elbow, habitual patterns of the patient, radiological joint involvement and to study pattern of compression neuropathy of the ulnar nerve.

1. INTRODUCTION

Hemophilia is a genetic disease caused by single gene mutation in X chromosome in which production of clotting factor VIII and factor IX is affected leading to recurrent joint bleeds. According to WHO, the prevalence of hemophilia globally is 1 in 10000 (1). Elbow is the second most common joint to bleed in patients with hemophilia after the knee joint (2). Recurrent bleeds lead to destruction of joint cartilage and reduced range of motion of the elbow joint.

The Ulnar nerve is a peripheral nerve arising from C8 and T1 segments of the cervical spinal cord. Its anatomical course behind the elbow joint axis places it at a risk of developing compression neuropathy. During day to day activities with normal motion of the elbow, the ulnar nerve is subjected to frictional injuries and compression which can occur at 5 anatomical points, which are: the Arcade of Struthers (a tunnel formed by fascia), just proximal to the medial epicondyle, the ulnar groove, the point between the humeral and ulnar heads of the Flexor Carpi Ulnaris (F.C.U) muscle and the point where the ulnar nerve leaves the F.C.U (3). Compression of ulnar nerve in this area leads to a nerve entrapment syndrome called Ulnar Neuropathy at Elbow (U.N.E) more commonly known, as cubital tunnel syndrome.

U.N.E is the second most common nerve entrapment syndrome after carpal tunnel syndrome. It is seen commonly in people like drivers, musicians and those in packaging in garment industries where prolonged elbow flexion attitude is required. It is also seen to occur in people with anatomical anomalies, post trauma (tardy ulnar nerve palsy), people with habitual leaning on the elbow, habitual excessive elbow flexion while sleeping, diseases affecting elbow ROM like rheumatoid arthritis and those causing swelling of the nerve like diabetes mellitus and Hansen's disease (4)(5)(6).

Many patients with hemophilia often complain of inability to write continuously due to fatigue and vague pain in hand and this is especially common in students during their exams.

Factors like restricted ROM of elbow, recurrent bleed and synovial hypertrophy causing compression of the ulnar nerve around elbow, faulty posture while sitting or sleeping and use of walking aids like elbow crutches can predispose them to develop UNE. However existing evidence of UNE in hemophilia is only from case reports and case series. A search for prevalence studies, review articles and RCTs on the same topic was made on Pubmed and Cochrane and no articles were found except for 1 case series and 3 case reports in international journals (2)(7)(8)(9). There is no data on prevalence of ulnar neuropathy at the elbow in persons with hemophilia and its correlation with various predisposing factors. Early detection of UNE can be managed by education regarding posture, care of elbow joint during bleeds, exercises and surgical correction preventing long term deformities and deficits in hand.

2. REVIEW OF LITERATURE:

1. Justification for the study.

2. Hemophilia – the disease.

3. Ulnar nerve course around the elbow joint and regional anatomy of cubital tunnel.

4. Ulnar Neuropathy at Elbow.

5. Ulnar Neuropathy at Elbow in Hemophilia

1. JUSTIFICATION FOR THE STUDY

Elbow joint is the second most common joint to bleed in hemophilia (10)(2) . U.N.E has been associated closely with conditions affecting the elbow joint such as rheumatoid arthritis and cubitus valgus defect post supracondylar humerus fracture. However on a literature search no studies about prevalence of UNE in hemophilia patients were found. Peripheral nerve entrapments are reported to occur in 4-19% of patients with severe hemophilia (2)(11) (12). The most common being femoral nerve entrapment following iliopsoas bleed. However reports of other nerves such as ulnar and median nerve entrapments have been reported as case reports(13)(14)(15)(16).

Many patients, most of them children and adolescents, attending the multispecialty hemophilia clinic in our hospital complained of inability to complete their answer papers during exams due to pain and discomfort while writing for long time. Spontaneous elbow bleeds occurring after writing exams for 2 to 3 consecutive days was also a common complaint. Such patients on examination showed signs of wasting of hypothenar muscles and the interossei compared to their normal hand. This observation led to a question - Is there a vicious cycle of chronic elbow bleeds causing compressive neuropathy of ulnar nerve which weakens the intrinsic muscles of the hand, which in turn causes over use of forearm muscles and increased pressure on elbow while writing; leading to recurrent elbow bleeds? As there is no documentation available on prevalence of U.N.E in hemophilia, it was decided to conduct a cross sectional study of the patients with hemophilia attending the hemophilia clinic in our hospital to find out the prevalence of U.N.E in them.

2. HAEMOPHILIA – THE DISEASE

Haemophilia is a hereditary disorder of coagulation caused by deficiency of clotting factors characterized by repeated episodes of bleeding, spontaneous or secondary to trivial trauma (1). Deficiency of factor VIII is called Haemophilia A and that of Factor IX is called Haemophilia B (Christmas disease). Haemophilia is an X linked hereditary disorder. The gene for factors VIII and IX are both located on the X-chromosome. The disease is seen exclusively in males who have a single X chromosome. Females are asymptomatic carriers as the normal X chromosome having normal factor VIII or IX gene provides about 50% of factor levels. Rarely in circumstances of excessive lyonization of the normal X chromosome, can a carrier female manifest with bleeding symptoms(17).

History of Hemophilia:

Hemophilia enjoys a reputation unlike many other hereditary diseases due to its association with the British royal family and the history of Europe. Queen Victoria (1837-1901) was a carrier and she had a son with hemophilia, Leopold and two daughters Alice and Beatrice who were both carriers. Alice was the grandmother of Alexis, the Tsaverich or heir prince of Russia, who suffered from hemophilia. He at that time could only be treated by the "mad monk Rasputin" with his hypnosis. The rising influence in courts of Russia, of Rasputin led to the Russian revolution in 1917AD(18)(17). The Jews were the earliest in history of hemophilia to identify the disease. They had a law enacted that if a woman's two male children died after circumcision then her third son will not be circumcised. This shows their recognition of the bleeding disease and females being carriers of the disease.

The first treatment for hemophilia was published in *The Lancet* in 1840, where a syringe developed by Dr.Blundell was used to take blood from a 'stout' woman and was transfused directly to the child who was bleeding profusely after a squint surgery. The bleeding stopped and child

survived (17). During World War II fractionation of the human plasma was discovered and the major components of the human plasma could be separated into different components. Cohn's fraction 1 was rich in factor VIII and fibrinogen(19). However risk of transmission of blood borne viruses is more with blood transfusion and plasma. It was impractical to use plasma as a substitute for factor VIII. The Bovine and later Porcine antihemophilic globulin (AHG, FVIII) were developed.

Cryoprecipitate was discovered by Judith Pool from USA who found out that if plasma was cooled to a very low temperature a cryoprecipitate rich in fibrinogen and FVIII was formed. During 1970s human lyophilized FVIII and FIX resulted in dramatic improvement in the treatment of haemophilia and the lives of hemophiliacs improved as they could self treat themselves at home as soon as spontaneous bleeds occurred. The epidemics of Hepatitis C and Human Immunodeficiency Virus (HIV) resulting from use of lyophilized human products acted as stimuli to achieve safe plasma derived products using viral inactivation processes. In 1984, the structure of F8 gene and the cloning of the gene were published in *Nature* (20). This discovery enabled the manufacture of recombinant FVIII and later recombinant FIX. But the success of managing hemophilia with recombinant factors in a safe and effective manner still cannot be celebrated as the incidence of inhibitors to the monoclonal factors is increasing and has now emerged as a big challenge in hemophilia care. Bleeds in hemophiliacs with inhibitors to FVIII/FIX have to be managed by recombinant FVIIa (NovoSeven) and Activated prothrombin complex concentrates (aPCCs) namely FEIBA (Factor Eight Inhibitor Bypassing Agent) and Autoplex-T (17).

Hemophilia – the genetics:

The human F8 gene, cloned between 1982 and 1984, is one of the largest described gene located by mapping on most distal band on long arm of X chromosome (Xq28) (21)(22). The gene defects found in hemophilia A are: gross gene rearrangements; insertions or deletions of genetic sequence of one base pair or up to entire gene; single DNA base substitutions resulting in amino acid

replacement (missense mutation), premature peptide chain termination (nonsense or stop mutations) or mRNA splicing defects. Gene rearrangement that consists of a unique inversion, is responsible for approximately 50% of hemophilia A(23)(17). Hemophilia B is caused by mutations in the F9 gene which lead to quantitative or qualitative deficiencies in circulating factor IX (FIX). F9 gene is located on Xq27.1 and it spans 33kbp. 64 % of the mutations causing hemophilia B is due to Missense/Nonsense mutation where a single nucleotide is replaced by another nucleotide. Other genetic defects associated are defective RNA splicing, small insertions/ deletions and gene rearrangements (24)(25). Hemophilia A and B are inherited in an X linked recessive pattern.

In 42-57% of cases there is no apparent family history and approximately 30% of newly diagnosed cases occur due to new mutation affecting the male propositus or the asymptomatic female carrier (26)(27).

The phenotypic differences between patients with similar genetic mutation in a single gene defect such as hemophilia is quite fascinating. In hemophilia the clinical diagnosis depends largely on the level of coagulation factor VIII or IX activity. Severe hemophilia has less than 0.01 IU/ml (<1%) of factor level, moderate hemophilia has factor level more than 0.01 IU/ml to 0.05 IU/ml (1%-5%) and mild hemophiliacs have factor levels more than 0.05IU/ml but less than 0.30IU/ml (5%- 30 %). On observing the cohorts of hemophilia patients it is seen that patients with severe hemophilia start bleeding earlier by age of 6 to 8 months(28). The age of onset of joint bleeds varies in severe hemophiliacs, between 6 months to 6 years. Moderate hemophiliacs also vary in their bleeding patterns and those with baseline factor of 2-3% have lesser bleed frequencies. This observation led to advocacy of prophylactic factor therapy to convert severe hemophiliacs into moderate hemophiliacs, in Sweden initially by Prof.Nilsson and later globally (29)(30) .

Haemophilic arthropathy – the pathophysiology:

The clinical manifestations of haemophilia depend upon the severity of the disease which in turn depends on the factor levels.

Prevalence of different types of bleeding in haemophilia is as follows:

Type of hemorrhage	Prevalence (%)
Haemarthroses	70-80
Muscle and subcutaneous haematoma	10-20
Other major bleeds (GIT/Throat/Neck/Compartment syndromes)	5-10
CNS Bleeds	< 5

Table 1: Prevalence of different types of bleeding in haemophilia(1)

Bleeding into the joint is termed as haemarthrosis. A joint that displays a tendency towards recurrent bleeding is called a "target joint". Once a target joint is established, complete resolution is not possible, there is a slow response to treatment predisposing for haemophilic arthropathy. The definition of a target joint is controversial and varies from country to country. In Canada, the generally accepted criterion is a minimum of three bleeds into a single joint within a consecutive three-month period(31)(32).

Haemophilic arthropathy may be defined as a condition associated with damage to joint cartilage secondary to repeated haemarthroses. The pathophysiology of haemophilic arthropathy involves multiple factors and multiple processes occurring in parallel or sequentially. Many studies advocate starting primary prophylaxis as early as possible after the first bleed to prevent haemophilic arthropathy and improve quality of life(33)(28)(34). The main function of cartilage is distribution of

compressive forces and to allow for a smooth, frictionless movement. It owes its function to its stable three dimensional structure. Any damage to this structure prevents the proper functioning of the cartilage. Haemophilic arthropathy, though shares a similar pathophysiology of cartilage destruction and synovial hypertrophy, has not been studied as well as other arthritic diseases such as rheumatoid arthritis, osteoarthritis, etc. The blood in the joint following an acute haemarthrosis is known to act as a stimulant for cartilage damage in multiple ways. Many in vitro studies postulated that the blood in the joint, specifically haemosiderin deposition acts as a trigger for synovial hypertrophy. Synovial macrophages help in removal of the iron from the RBCs after a haemarthrosis. Deposition of haemosiderin or iron in the synovial lining (in the form of discrete granules) and the supporting layer (in the form of dense aggregates) has been demonstrated characteristically by arthroscopic studies and animal studies. The iron deposition leads to synoviocyte hypertrophy (resulting in formation of synovial villi), and neovascularization in the subsynovial layer. The highly vascular and hypertrophic synovium becomes easily entrapped within the joint, increasing the risk of recurrent hemorrhage. Recurrent haemarthroses perpetuate synovial inflammation, creating a vicious cycle of haemarthrosis-synovitis-haemarthrosis (35)(36).

It is unclear whether the haemosideritic synovium acts a trigger for chemokine production or whether the increased macrophages in the synovium cause it. The secondary damage of the joint cartilage is secondary to production of chemokines such as Interleukin1 (IL-1), IL-6 and Tumor Necrosis Factor-Alfa (TNF-ά). But the synovial concentration of chemokines in synovial fluid from cases of hemophilic arthropathy is found to be much lesser than in inflammatory arthritis such as rheumatoid arthritis(37). Corroborative evidence of synovitis secondary to haemosiderin deposition was also seen in the study on pigmented villonodular synovitis(38). Studies suggesting synovitis preceding the cartilage destruction recommend strategies for early detection of synovitis and treatment of chronic synovitis by synoviorthesis to preserve joint cartilage. Many studies question whether synovitis secondary to haemosiderin deposition is the only cause for cartilage damage. The

human articular cartilage is made of fewer chondrocytes dispersed in a relatively large extracellular matrix made only of proteoglycans and collagen. The delicate balance between synthesis and breakdown of collagen continuously causes turnover of the matrix material. Few studies have shown that exposure of cartilage to blood for a brief duration (It takes 4 days for blood to clear from joint cavity) was seen to inhibit matrix synthesis and caused breakdown of the matrix. The blood in the joint cavity through the combined action of mononuclear cells (by their lysozomal enzymes and catabolic chemokines) and the RBCs (source of iron) causes direct damage to the cartilage. It is mediated by toxic hydroxyl products formed by iron catalyzed conversion of oxygen metabolites formed by mononuclear cells. It has been demonstrated by in-vitro studies and by canine studies that the cartilage damage occurs much before the synovial changes are seen(39)(40). Due to combination of recurrent haemarthrosis and synovitis, the collagen network in the articular cartilage, which is responsible for its tensile strength, is disrupted. This makes the joint and the underlying bone biomechanically susceptible to micro trauma and secondary damage.

Hemophilic arthropathy of elbow – stages, special considerations, complications and management:

Clinically, the progression of hemophilic arthropathy in elbow joint can be classified into 4 major stages:

1. Stage of acute haemarthrosis: Characterized clinically by rapid bleeding into the joint. This stage is usually accompanied by a prodrome of stiffness, tingling, and pain. Acute haemarthrosis usually resolves without any synovial changes by 2 weeks, and usually requires factor administration for early resolution. However the repeated bleeding episodes overwhelm the absorptive capacity of synovial membrane.
2. Stage of chronic synovitis: Synovial hypertrophy leads to thickened synovial membrane. This is associated with enlargement of head of radius and secondary impingement with mechanical block to forearm pronation and supination.

3. Stage of early arthritis: Partial loss of joint cartilage and slight restriction of elbow flexion and extension occurs in this stage.
4. Stage of end arthritis: Complete loss of joint cartilage in radio-humeral and ulno-humeral joints. Severe range of motion (ROM) restriction in the joint.

Each stage presents with different challenges and requires a different management approach. But since none of the events are sequential or unidirectional, and overlapping of features are seen many other functional classifications or scores individualized for elbow joint were later introduced.

Hemophilic arthropathy of elbow joint and compressive ulnar neuropathy:

The densely pigment-stained, hyperplastic synovial membrane that is usually seen in chronic hemophilic synovitis, undergoes metaplasia to a dense fibrous tissue with reduced elastic capabilities. This phenomenon is commonly known as arthrofibrosis. Overtime, the ulnar groove deepens, resulting in ulnohumeral impingement. The combination of arthrofibrosis and bony impingement results in a reduced flexion-extension arc with increased severity of the pain and range of motion limitation. Patients can experience an ulnar neuropathy as a result of chronic synovitis impinging on the ulnar groove(36).

Plain X ray studies have been used for a long time in assessment of hemophilic arthropathy. The radiographic changes seen in hemophilic elbows specifically include: enlargement of the radial head, narrowing of the joint spaces at both, the radio-humeral and ulno-humeral joints, irregularities at the proximal radio-ulnar joint, deepening of the humeral trochlea, presence of medial osteophytes or spurs, and angular deformities. Three types of radiographic patterns have been described in hemophilic elbow arthropathy: (41)

1. Predominantly lateral joint involvement: an enlarged head of radius, reduced radio-humeral joint space, an irregular proximal radio-ulnar joint, and formation of subchondral cysts on the lateral portion of the humerus.

2. Predominantly medial joint involvement: reduced ulno-humeral joint space, deepening of the ulnar trochlea, medial spurs.
3. Global arthritis: involves both lateral and medial aspects of the joints.

Among the many classifications used for radiological evaluation of the hemophilic elbow arthropathy, the Pettersson classification has been recommended by the Orthopedic Advisory Committee of the World Federation of Hemophilia as the preferred radiographic classification system(42) Pettersson score is an additive system based on the presence or absence of eight specific radiographic features which are osteoporosis, epiphyseal enlargement, subchondral irregularities, narrowing of joint space, subchondral cyst formation, joint erosions, joint incongruence and joint deformity. Many studies support the use of radiological criteria for evaluation of the stage of hemophilic arthropathy and to evaluate the efficacy of various treatment modalities in limiting the progress of the disease.

But, the elbow being a complex joint with multiple articular surfaces, the reliability of the radiological scores is often questioned by many studies(43)(44). Ultrasound, Magnetic Resonance Imaging (MRI) have also been used for evaluation of the hemophilic arthropathy(45)(46).

Management of hemophilic arthropathy of elbow joint has challenges unique to the joint. The management of acute haemarthrosis involves early factor administration, controlling the joint bleed, resting the joint in neutral position and early structured exercise therapy aimed at improving the muscle strength, restoring elbow range of motion and improving elbow proprioception. When the joint reaches the stage of chronic synovitis, factor replacement will not suffice. It has been seen in a study that despite regular factor replacement for up to 9 months in patients with chronic synovitis, only 40% of the patients had relief from recurrent bleeds(47). Synovectomy is the treatment of choice at this stage to prevent recurrent bleeds, reduce the frequency of factor administration and prevent progression of joint cartilage destruction. In early

days, open synovectomy was practiced which required prolonged stay in the hospital, was associated with surgery related complications and requirement of prolonged factor replacement made it expensive. Hence despite achieving up to 85% reduction in rate of repeated bleeding, it was not practised (48). Arthroscopic synovectomy later replaced open synovectomy, which showed the same efficacy as open synovectomy in reducing episodes of haemarthrosis. In a study done by Dunn et al, arthroscopic synovectomy led to reduction of frequency of joint bleeds by 84% among the 64 subjects enrolled in the study (29 among them had chronic synovitis of elbow)(49).

Less invasive synoviorthesis by various chemical and radio isotope injections are more popular now. Chemical synoviorthesis uses various agents for intra articular instillation like methyl prednisolone, osmic acid, rifampicin and oxytetracycline. They are believed to have proteolytic effects that cause subsynovial fibrosis, which reduces the inflammation and hyperemia of synovial proliferation. Thus it protects the joint from repeated episodes of haemarthroses and slows the degeneration of joint cartilage by breaking the bleed-synovitis-bleed cycle. Many independent studies have proven efficacy of intra articular rifampicin and oxytetracycline(50)(51). The radioactive synovioarthesis primarily use radio isotopes that emit Beta rays which penetrate up to depth of 4-6 mm destroying the hypertrophic synovium with the clinical outcome as good as chemical synovioarthesis. There has been no report of any pre-malignant/malignant changes in joints after radio isotope injection. The isotopes used for radioactive synovioarthesis are gold (Au-198), Yttrium(Y-90), Rhenium(Re-186), Dysprosium (Dy-66) and Phosphorus (P-32 /chromic phosphate)(36). The efficacy of Yttrium -90 isotope has been evaluated in various studies and has been found to be efficacious in up to 85%of injected joints (52) (53).

A complication associated with chronic synovitis stage in hemophilic elbow is enlargement of head of radius. The enlarged rough head of radius impinges on the ulno humeral joint and acts

as a mechanical block to forearm pronation. As much as 20 degrees of limitation of pronation is seen by an age of 15 and the limitation increases with age. Limited elbow pronation hampers many activities such as bathing, toileting, writing and eating. As a treatment, excision of radial head is advised in such patients for relief of pain, limiting chronic arthropathy and treating disabling restriction of elbow ROM. Though ideally it is advised in people with nearly normal ulno humeral joint cartilage with limited restriction of flexion-extension in elbow joint, many a times ulno humeral cartilage changes are seen concurrent with radial head enlargement. Before planning radial head excision it has to be confirmed that the cause of pain/ restricted ROM is actually being caused by enlarged radial head. Pre operative radial nerve conduction studies are advised as risk of injury to radial nerve is present during the procedure. A standard Kocher approach is usually used for radial head excision with care to prevent damage to radial nerve and preserving the annular ligament. The procedure has been shown to provide sustained pain relief, reduction in the frequency of bleeding, and improvement in forearm ROM in people with advanced hemophilic arthropathy of the elbow(54,55).

Elbow flexion contractures can occur secondary to the flexed protective position in which, the patients rest to reduce pain during acute bleed and also due to ulno humeral joint involvement. The surgical release of elbow contractures by anterior capsulotomy as done in patients with non hemophilic elbow arthropathy have not shown the same successful results in hemophilic elbows. The hemophilic elbow arthropathy due to the following reasons often fails to respond to soft tissue release: associated decreased joint space, the presence of incongruent articular surfaces, subluxation of the ulno humeral joint, the presence of heterotopic ossification and the presence of long-term contractures. Ulno humeral joint arthroplasty has been advocated as a better alternative to capsulotomy in non hemophilic elbow arthropathies in which the impingement at the joint is relieved by drilling holes in coronal process of humerus. There is however no substantial evidence about use of similar procedure in haemophilic arthropathy. The patients suffering from

global arthritis of elbow, total arthroplasty of elbow joint has been tried. Evidence is only in the form of a few case reports. Infection is the main complication after total elbow arthroplasty(56). In two case series published by two independent researchers Kamineni et al. and Chapman et al, of 12 elbow arhroplasties, 3 patients had infection and ulnar nerve paralysis, axillary vein thrombosis. Persistent pain was present in one patient each(56). The goals of pain free, functionally mobile elbow joint can be achieved by synovectomy and radial head excision with much lesser complications than total elbow arthroplasty.

3. ULNAR NERVE AND THE REGIONAL ANATOMY OF CUBITAL TUNNEL:

The ulnar nerve is called so due to its close relation to the ulna along its course in the forearm. The spinal nerves C8 and T1 and inconsistently C7 contribute to form the ulnar nerve fibers. These fibers travel as part of the lower trunk and later the medial cord of brachial plexus. The ulnar nerve arises from medial cord at the level of axilla. In the axillary area, it lies along its lateral walls and continues along the medial aspect of arm. In the proximal half of the arm it is closely related to the brachial artery, median and radial nerves. Midway along the arm it pierces the medial inter muscular septum and enters the posterior compartment of arm. "Arcade of Struthers" is a thin, filmy tissue attached to the inter muscular septum, which can occasionally be thick and can compress the ulnar nerve. The compression due to Arcade of Struthers is not universally agreed upon(57,58). As the ulnar nerve descends down it lies posterior to medial head of triceps and humerus. At distal part of arm it enters the groove formed by medial epicondyle usually called as condylar groove or retrocondylar groove. The nerve is very superficial as it passes along the retrocondylar groove.

As it emerges out of the groove it enters the medial compartment of forearm after passing beneath the humeroulnar arcade and passing through the Flexor Carpi Ulnaris (F.C.U) muscle (59,60). The tunnel like structure through which the ulnar nerve traverses, whose roof is formed by aponeurotic arch and muscle fibers of F.C.U and floor by medial ligaments of elbow and muscle fibers of F.C.U, is called as cubital tunnel. Cubit in latin means the region of elbow and forearm. The French name of ulnar nerve is *le nerf cubital* which translated means cubital nerve. The ulnar nerve emerges out of the cubital tunnel through aponeurosis lining the deep surface of F.C.U. It reaches the wrist well protected within layers of F.C.U. At wrist, the ulnar nerve passes through Guyon's canal which in reality is a tunnel formed between hook of hamate, pisiform bone. The other name for Guyon's canal is the ulnar tunnel. The floor of the tunnel is formed by transverse carpal ligament

and pisohamate ligament, the palmar fascia and its extension as volar carpal ligament along the palmaris brevis muscle. The ulnar nerve shares the ulnar tunnel with ulnar artery and fat. The nerve divides into the superficial and deep terminal branches within the ulnar tunnel.

Branches of the ulnar nerve:

The ulnar nerve does not branch in the upper arm. Below the elbow, it gives its first branch to F.C.U about 10 cms distal to medial epicondyle. A variation of branch to F.C.U arising proximal to medial epicondyle is seen occasionally. It later gives a branch to ulnar half of flexor digitorum profundus muscle. The palmar cutaneous branch arises in the mid forearm, runs distally along the volar aspect of forearm and wrist superficial to Guyon's canal. It supplies the proximal half of ulnar border of the palm. The dorsal cutaneous branch arises 5 cms proximal to wrist, winds around the ulna and innervates the ulnar side of dorsum of the hand and dorsal surfaces of half of fourth and whole of fifth digits. Dorsal cutaneous branch anamolously can arise from the superficial radial nerve.

The ulnar nerve divides into superficial and deep terminal branches within the Guyon's canal. The superficial terminal branches gives the following branches: branch to palmaris brevis, branch to skin of distal ulnar border of the palm, two digital nerves that innervate skin over palmar surface of medial one and half digits. The deep branch gives the following branches: motor branches to opponens digiti minimi, muscles of hypothenar eminence, lumbricals third and fourth, all the palmar and dorsal interossei, adductor pollicis and inconsistently to flexor pollicis brevis.

Regional anatomy of the cubital tunnel:

Ulnar nerve, as it passes around the elbow can get compressed at multiple points. The compression due to thick Arcade of Struthers has been reported but has been challenged by many also. Within the retrocondylar groove chance of damage to the ulnar nerve due to mechanical or traumatic causes is increased. The aponeurotic arch of the F.C.U muscle also known as "humeroulnar arcade" or "Osborne's ligament or band" is formed by the attachment of the F.C.U to the medial epicondyle and

to the olecranon (61). The edge of the "humeroulnar arcade" usually lies about 1 centimeter distal to a line joining those points. The cubital tunnel is present within the belly of F.C.U with a roof formed by muscle fibers and aponeurotic arch and floor formed by the medial ligaments of the elbow and F.C.U muscle fibers.

The dynamic anatomy of ulnar nerve at the elbow is important to know to understand the pathophysiology of U.N.E. When elbow is extended the shape of cubital tunnel is almost circular and spacious enough. On flexion of the elbow, increase in the distance between medial epicondyle and olecranon by about 1 cm causes F.C.U aponeurosis to tighten over the nerve. The shape of cubital tunnel during flexion becomes wider and flatter. Along with this the medial elbow ligaments bulge, flatten the retrocondylar groove and the medial head of triceps pushes the nerve more posteriorly. The tunnel narrows by about 55% with extreme elbow flexion with the ulnar nerve stretched tightly around the medial epicondyle. Cadaveric studies have demonstrated increase in intra and extraneural pressure pressures when elbow was flexed beyond 90 degrees (60). Similar changes in pressure have been documented in patients undergoing surgery for U.N.E. Due to absence of corresponding values from controls the ambiguity about clinical significance of increased pressure cannot be demonstrated. Sometimes an anomalous slip of anconeus muscle arising from triceps and the olecranon inserting upon the medial epicondyle, called the anconeus epitrochlearis is seen. This muscle has been found in 10 % of people in cadaveric studies and it usually crosses over the ulnar nerve in the condylar groove (62). Supracondylar spurs and fibrous bands bridging the medial epicondyle and olecranon are also the lesser known culprits causing compression of the ulnar nerve around the elbow region.

Ulnar neuropathies in axilla and wrist:

The ulnar nerve can less frequently be damaged in the axilla and the upper arm, usually in combination with radial and median nerves, and is called "triple neuropathy". The compression can occur due to mechanical causes such as crutches, tourniquet, during sleep/coma/drunken sleep when the arm hangs over a sharp edge, aneurysms/pseudoaneurysms in brachial artery, haematoma, and compartment syndromes following trauma. The ulnar nerve can get damaged secondary to trauma associated with anterior shoulder dislocation, fracture of proximal humerus and secondary to injection associated injury. Rare causes for ulnar neuropathy in axilla are ischaemia from fistula created in upper arm for haemodialysis, nerve tumors, multifocal motor conduction block neuropathy and neuropathy as a part of brachial plexopathy.

At the level of wrist, the ulnar nerve can get compressed, as it passes through "Guyon's canal", where the main nerve or the terminal branches can get compressed. The deep terminal branch can get compressed just distal to Guyon's canal, which can produce motor weakness in all ulnar innervated muscles without any sensory loss. The deep terminal branch after innervating hypothenar muscles can get compressed causing isolated weakness of lumbricals, interossei and thenar muscles. This pattern is the most frequently seen ulnar neuropathy at wrist. The sensory superficial terminal branch of the ulnar nerve can get compressed within Guyon's canal producing only sensory loss. The common causes for ulnar neuropathy at wrist are repetitive stress injury due to occupations and leisure activities. It is commonly seen in cyclists. A study in 25 long distance cyclists showed that after a long distance cycle hike 14% had a sensory abnormality in the 5th digit and intrinsic muscle weakness was seen in 22% of the individuals. Padded gloves, padded handle bars and frequent position changes of wrist over the handlebars is advised for prevention of the "cyclist's palsy". Other professions at similar risk are pizza cutting, people operating a computer mouse for a long period,

people engaged in prolonged videogames, wheel chair propellers and people engaged in wheelchair sports. Ganglia and other mass lesions like lipomas, rheumatoid synovial cysts, tumors like chondromas, schwanomas and villonodular tenosynovitis are less common causes for compressive ulnar neuropathy at wrist. Rare causes include abnormal intrinsic hand muscles, abnormal ligaments, non united hook of hammate and scleroderma associated calcinosis.

4. Ulnar neuropathy at the elbow(U.N.E):

The famous sculpture of "The Thinker" by Auguste Rodine (1879- 1889) might be one of the masterpieces of modern day sculptures, but the amount of compression the man's ulnar nerve would be undergoing due to continuous flexion and pressure secondary to the posture in which he is sitting is unimaginable (63). If he was alive, "The Thinker" would have definitely suffered from U.N.E. Ulnar neuropathy at elbow (U.N.E) is an appropriate, all inclusive and general term for the heterogenous focal neuropathies where ulnar nerve gets affected around the elbow joint. The prefix "idiopathic" is added when no exact etiology can be found.

The many synonyms used for U.N.E include cubital tunnel syndrome, tardy ulnar palsy, cell-phone elbow, traumatic ulnar neuritis, compression neuritis of the ulnar nerve and Feindel-Osborne syndrome. The more popular term "cubital tunnel syndrome was proposed by Feindel and Stratford (64). Tardy Ulnar palsy refers to a slow, chronic deterioration of ulnar nerve function months to years after trauma to the elbow. The term cubital tunnel syndrome oversimplifies the ulnar neuropathy at the elbow, which may be due to a number of factors other than compression within the cubital tunnel, such as recurrent subluxation of the ulnar nerve out of its groove, or entrapment proximal or distal to the cubital tunnel.

The U.N.E is second most common compressive neuropathy after carpal tunnel syndrome. However data about global or national annual incidence is not documented in many studies. Of the very little epidemiological data about U.N.E, one study from the province of Sienna in Italy reported that U.N.E had a standardized annual incidence of 21 per 100000. Its incidence was $1/13^{th}$ of that of carpal tunnel syndrome. Another study done in a cohort of 179 female floor cleaners showed after clinical and electrophysiological studies that 48.3% of them had carpal tunnel syndrome and mild U.N.Es occurred in 6.8%.

U.N.E secondary to trauma can occur as direct injury to the nerve, iatrogenic injury during surgery or secondary to complications like scarring or deformity of elbow joint. The fractures of distal humerus is associated with upto 3.2% chance of acute ulnar neuropathy as seen in a study done on 320 subjects with fracture humerus (65). Iatrogenic procedures like percutaneous cross-pinning for distal humerus fractures are more frequently associated with ulnar neuropathy. Cubitus valgus deformity occuring as a complication following poorly reduced supracondylar fracture of humerus is associated with tardy ulnar nerve palsy (66,67). Following the healing of fractures, the regional anatomy of the retrocondylar groove is altered which renders the ulnar nerve less protected from exposure to external pressure. Diseases that affect the elbow joint are also associated with U.N.E. A few examples are severe rheumatoid arthritis, osteoarthritis, Paget's disease and congenital anomalies of elbow associated with shallow condylar groove and cubitus valgus deformity(68). U.N.E due to external pressure is seen secondary to the compression of the ulnar nerve in the condylar groove due to its superficial and unprotected course.

Elbow flexion narrows the cubital tunnel, pushes the ulnar nerve more exteriorly and increases the susceptibility to damage by external pressure. Prolonged flexion causes repetitive episodes of minor increase in pressure on the nerve. Habitual leaning over the elbow on hard surfaces, prolonged use of telephone while leaning the inner aspect of elbow over the desk, resting the flexed elbow over window of the car while driving long distances, supporting the head with flexed elbow while reading or watching television, wheelchair users who rest their flexed elbows over unpadded arm rests, crutch users loading on a flexed elbow for a long time, bed bound individuals whose elbows are kept flexed for long periods are all examples of patterns leading to U.N.E. Prolonged or repetitive elbow flexion without any elbow pressure, as seen while sleeping with arm tightly flexed and vocations which requires working for long time with flexed elbows is often associated with sensory symptoms like numbness or paraesthesia in ulnar

distribution. However establishing a cause and effect relationship between a particular vocation and U.N.E has been difficult, which is the case with many vocation related neuropathies.

Other less common causes for U.N.E are ganglia, lipoma and epidermoid cysts present within the condylar groove or cubital tunnel. U.N.E is seen secondary to synovial hypertrophy due to rheumatoid arthritis, giant cell tumors in the region and synovial cysts (14,69). Supracondylar spurs, though often associated with U.N.E, their presence in only about 1% of population and the location commonly being a few centimeters above the medial epicondyle, make them a rare cause. They are more often associated with median neuropathy. Compression of ulnar nerve at the edge of FCU aponeurosis is commonly seen. Diseases such as diabetes mellitus and leprosy are also associated with U.N.E.

The ulnar nerve is one of the most common nerves to be damaged after surgery involving general anaesthesia and most of the times, the cause is U.N.E. After detailed study it has been found that U.N.E can develop anytime from the preoperative period to the convalescence period at home. Hence the term "post anaesthetic ulnar neuropathy" is replaced by the term "perioperative ulnar neuropathy". Perioperative U.N.E was studied in detail by Wadsworth and recommendations for safe positioning of the hand during surgeries, use of paddings for ulnar nerve were suggested by him and his contemporaries (70). However a review article by Stoelting concludes that the incidence of perioperative U.N.Es did not reduce significantly despite all the precautions (71).

Clinical features of U.N.E:

The most common symptoms reported by patients suffering from U.N.E in the previous studies are sensory symptoms in the ulnar nerve innervated parts of hand and forearm. Pain in the elbow region, along the distribution of ulnar nerve and tenderness over inner elbow are more commonly complained than paraesthesia with symptoms being more common at night or on prolonged

elbow flexion (72,73). Motor symptoms may vary from no symptoms at all to having profound weakness of hand muscles. Some patients, especially diabetics have no sensory symptoms at all but show progressive wasting of the hand muscles(74).

The sensory examination for U.N.E should ideally involve examination of sensation of light touch and pain in cutaneous territories of each of the three sensory branches of the ulnar nerve. The dorsal and palmar ulnar cutaneous nerves which are branched from ulnar nerve before nerve entering the Guyon's canal, if involved indicate ulnar neuropathy proximal to wrist. Sensory abnormalities extending more than about 2 cms proximal to the wrist crease indicates involvement of medial cutaneous nerve of forearm/ brachial plexus / T1 nerve root. Wasting of ulnar innervated lumbricals and dorsal interrosei is seen in patients with severe U.N.E, causing an ulnar claw hand deformity. Muscle cramps, fasciculations and sometimes focal dystonia have been described in patients with U.N.E (75,76). Chronic entrapment of ulnar nerve is associated with motor symptoms like loss of dexterity, reduced grip and pinch strength.

Many clinical signs have been described for ulnar neuropathy. Apart from their historical importance they have very less value in diagnosing U.N.E. The provocation tests for ulnar neuropathy are based on a premise that local ischemia causes axonal hyperexcitability and lowered membrane threshold for action potential. Thus the provocation tests, literally provoke an ectopic action potential to produce a sensory or motor symptom (75). Suderland in his studies mentioned that the ulnar nerve fascicles supplying sensation in hand and motor fibers innervating intrinsic muscles are located superficially at medial epicondyle, while those innervating F.C.U and ulnar half of Flexor Digitorum Profundus (F.D.P) lie deeper (77). This finding explains the frequently involved hand weakness and less frequently involved F.C.U and F.D.P weakness in U.N.E. It also explains early sensory complaints frequently seen in U.N.E. Positive provocative tests in some cases might be the only evidence of ulnar nerve entrapment in some cases with normal electrodiagnostic tests. The reason behind this may be that nerve conduction studies use

electrical stimulation which selectively stimulate large diameter myelinated axons, but ulnar nerve pathology is present in small and medium axons.

Provocation tests done for U.N.E are Elbow Flexion Test (E.F), Pressure test, Combined Pressure and Flexion test (C.P.F) and Tinel's sign. The C.P.F test involves putting elbow in maximum flexion and applying an external pressure just proximal to cubital tunnel for 60 seconds. Presence or worsening of paraesthesia/numbness in ulnar distribution indicates U.N.E. Sensitivity of tests were higher when pressure was applied for 60 seconds (98%) than when applied for 30 seconds (91%) and conversely specificity was more with 30 seconds pressure application (97%) than with 60 second application (95%) (75). Elbow flexion (E.F) test involves the subject actively fully flexing the elbow, keeping the forearm supinated and wrist at neutral position for usually upto 60 seconds and symptoms of paraesthesia and numbness indicate U.N.E. The 60 second E.F test has a specificity of 99% and sensitivity of 75%. The pressure test or pressure provocative test involves putting external pressure proximal to cubital tunnel with the elbow in 20 degrees of flexion forearm in supination for 60 seconds and reproduction of patient's symptoms indicate U.N.E. It has sensitivity of 89% and specificity of 98% (75).

Tinel's sign was described by Jules Tinel in 1915 as a sensation in the distribution of sensory or mixed peripheral nerves after percussion over the newly formed axons. For U.N.E Novak and Mackinnon recommended tapping along the course of ulnar nerve proximal to cubital tunnel and progressing distally. Distal progression of sequential Tinnel's sign is considered a sign of neuronal recovery and it was first suggested by Napier. A study by Novak et al reported 70% specificity and 98% specificity for Tinel's sign. Though various methods of percussing the nerve exists in literature, tapping with index finger is recommended. Motor Tinel's sign was first described by Montan and Liguroi. On tapping the nerve along its course if an "involuntary motor jerk" is seen in the ulnar nerve innervated muscles it is suggestive of U.N.E. Kingery et al

investigated 50 cases with ulnar neuropathy and reported that motor Tinel's sign has a sensitivity of 78% and specificity of 79%.

Many signs have been described to demonstrate ulnar nerve weakness in different muscles supplied by ulnar nerve. The motor signs and tests of ulnar nerve involving Adductor Pollicis (A.P) are Froment's sign and Jeanne's sign. Those involving the interossei are First Dorsal Interossei screening test (F.D.I), finger flexion test, crossed finger test and Egawa's sign. The ulnar nerve signs involving the ulnar nerve innervated lumbricals are Duchenne's sign and Andre – Thomas sign. The ulnar nerve signs involving the hypothenar musculature are Wartenberg's sign, Masse's sign, Pitres- Testut sign and Palmaris Brevis sign. The motor ulnar nerve sign involving the ulnar supplied part of flexor digitorum profundus is Nail file sign.

Froment's sign was described by Froment in 1915. A positive Froment's is characterized by compensatory flexion of the interphalangeal joint of thumb by action of anterior interosseous nerve innervated flexor pollicis longus, during a lateral pinching activity using a paper. The sign can be false negative due to action of extensor pollicis longus that allows patient to stabilize the paper without flexion of the IP joint. This can be overcome by performing the test in slight wrist flexion which eliminates the ability of extensor pollicis longus to act as a thumb adductor. Patients with chronic ulnar neuropathy tend to develop joint laxity in the first metacarpal joint through substitution patterns to compensate for weak A.P muscle. Jeanne's sign is considered positive if hyperextension of MCP joint occurs as compensation to weak lateral pinch due to A.P weakness. The Froment's sign and Jaenne's sign are mutually exclusive signs. Wartenberg's sign refers to the impossibility to fully adduct the extended little finger with wrist in neutral and forearm fully pronated. Comparison to the normal side helps in the diagnosis. Wartenberg's sign has been known as a late manifestation of the ulnar nerve palsy. The tests described above and other tests mentioned, have been described elaborately in literature, but their validity and reliability has not been tested adequately by studies (75). Provocative testing and systematic

assessment of motor and sensory functions of ulnar nerve are important aspects of a comprehensive clinical assessment for U.N.E.

U.N.E – Electrodiagnostic studies:

The goals of electrodiagnostic studies are to confirm that nerve damage is confined to ulnar nerve, to localize the lesion and to assess severity. For diagnosis of UNE, motor nerve conduction studies are performed by recording from an ulnar innervated muscle and stimulating ulnar nerve at wrist, below and above the elbow. Changes in amplitude, slowing of nerve conduction velocity (NCV) and dispersion of the compound motor action potentials (C.M.A.P) are diagnostic of U.N.E. The electrodiagnostic evaluation of U.N.E is complex and challenging even to the most experienced experts. The American Association of Electrodiagnostic Medicine (AAEM) Quality Assurance Committee has developed guidelines for practice parameters for electrodiagnostic studies in U.N.E (78). The recommendations to be followed as practice standard to diagnose U.N.E include-

1. The ulnar sensory and motor NCS should be performed with surface stimulation and recording with limb temperatures being monitored and maintained in a reference range. Limb temperatures outside the reference range have to be reported.
2. If ulnar sensory or motor action potentials obtained are abnormal, further NCS should be done to rule out any diffuse process.
3. Ulnar motor NCS reports should specify the elbow position used during the test. Moderate flexion of elbow between 70 degrees to 90 degrees is recommended.

The following recommendations are practice guidelines which when followed indicate U.N.E with moderate degree of clinical certainty:

1. Across elbow distances with elbow in moderate flexion must be in the range of 10 cms. Studies suggest this distance correlates best with the published reference values.

However chance of missing a focal defect is more when latencies are measured across 10 cms distance.

2. Stimulation below elbow should not be more than 3 cm distal to the medial joint as the ulnar nerve at that point is deep to F.C.U muscle which increases risk of sub maximal stimulation.
3. Multiple internally consistent abnormalities are more convincing than isolated abnormalities which raise the possibilities of technical errors. U.N.E is considered if the following are observed (mentioned in the order of strength of evidence):
    a. Absolute motor NCV from above elbow (AE) to below elbow (BE) segment is less than 50 m/s.
    b. An AE-to-BE segment NCV is slower by more than 10m/s than the BE-to-wrist (W) segment.
    c. Decrease in CMAP negative peak amplitude from BE to AE is more than 20 %, presuming anomalies of Martin-Grubber anomalies are not present.
    d. A significant change in CMAP configuration at AE compared to BE site, presuming anomalies of Martin-Grubber anomalies are not present.
    e. Sensory Nerve Action Potential (SNAP) recording from the fifth digit, may aid in diagnosis but changes like loss of amplitude are nonspecific and non-localizing for U.N.E.
    f. When ulnar NCSs from ADM muscle are inconclusive, it is recommended to perform NCSs from FDI muscle considering differential fascicular involvement. Inching studies exploring for changes in CMAP amplitude/ latency/ configuration over precisely measured 1 or 2 cms increments between AE and BE, is also considered specific.

g. In severe UNE, Wallerian degeneration affects the distal segment of ulnar nerve. In such cases comparing axilla-to-AE segment with AE-to-BE segment may be useful but normative data about the same is scant.
h. NCSs to forearm muscles FCU and FDP are not generally useful.
i. Needle EMG if indicated must always include the FDI muscle which most frequently shows abnormalities in U.N.E and should include FCU and ulnar innervated FDP muscles. Normal EMG in forearm muscles however doesn't rule out UNE in favor of wrist lesion due to possibility of differential fascicle involvement within ulnar nerves (78).

Role of Ultrasonography and MR imaging in U.N.E:

Ultrasonography in diagnosing U.N.E has been used in many studies. Measuring the swelling of the ulnar nerve, ratio of swollen section of ulnar nerve to the normal section and cross sectional area of cubital tunnel has been found to be useful in studies. In a study by Beekman et al involving 82 cases of U.N.E and 9 probable cases of U.N.E where both electrodiagnostic studies and Ultrasonography (USG) were done, it was seen that patients with U.N.E had a significantly larger diameter of ulnar nerves than controls and sensitivity of USG was 80% and specificity was 86% (79,80). Volpe et al evaluated 50 elbows with U.N.E comparing maximal cross sectional area with a control group. The study showed strong correlation between the maximal cross-sectional area and severity score of U.N.E (81). Initially MRI was indicated in evaluation of U.N.E to search for clinically undetectable elbow joint damage, gangliomas and other soft tissue masses. MRI abnormalities mainly change in signal intensities and nerve enlargements are confirmatory of U.N.E. The study by Vucic et al showed that MRI changes were seen in 90% of patients with U.N.E while electrodiagnostically only 63% of the patients were diagnosed (82). MRI has been favored more since it can exactly localize the compression to retroepicondylar groove, cubital tunnel, distal forearm and combination of these sites. Even a diffuse ulnar nerve

disease can be easily diagnosed on MRI and hence it is being seen as a valuable pre surgical investigating tool.

Differential Diagnosis of U.N.E:

U.N.E must be distinguished from disorders of the spinal cord, nerve roots, brachial plexus, and small lacunar cerebral infarcts. Conditions mimicking U.N.E in clinical features are amyotrophic lateral sclerosis (distinguished by extensive motor involvement with no sensory involvement), benign monomelic motor neuron disease (anterior horn cell disease without the severity and progressive nature of ALS), multifocal motor neuropathy (involves ulnar innervated muscles preferentially, but lacks sensory symptoms), syringomyelia (wasting of intrinsic muscles of hand is frequently seen, but the pain, motor and sensory impairment is usually more extensive than U.N.E) , C8 radiculopathy/ myelopathy (it is uncommon but can be distinguished by weakness in non ulnar innervated muscles supplied by C8 nerve root like triceps, extensor carpi ulnaris, extensor digitorum, etc), Brachial plexopathies (distinguished by involvement of radial and median nerves, Horner's syndrome when C8 root is involved) and lacunar infarcts in thalamus or corona radiate (mimics sensory-motor symptoms of UNE) (74).

Management of U.N.E:

As the clear natural history of U.N.E has not been documented properly, there are no clear guidelines regarding management. The main aim of management is prevention of further damage to ulnar nerve and treatment of the cause of compression. The conservative management involves use of exercises, splints, behavioral modification and changing the ergonomics at work place. The conservative management follows a rational plan of management. The first step is educating the patient about the ulnar nerve location, asking about the habitual patterns of leaning on the elbow, sleeping with flexed elbow, etc. External padding, sports elbow pads, cushioned arm rests in wheelchairs and chairs are simple measures to reduce the external pressure on ulnar nerves. The

pads can be worn at night with padding over the flexor aspect to prevent flexion and during day time over padding can be placed on extensor aspect to protect the nerve from external pressure. Adequate precautions about elbow positioning can prevent perioperative ulnar neuropathy. Most patients with mild to moderate UNE (Mc Gowan Grade 1 and Grade 2) respond well to conservative management.

Delaying the surgery when indicated and continuing only conservative measures can lead to further damage. Hence evaluating with CT/MRI is recommended to rule out any structural anomalies. Surgical correction is required in severe cases. The simplest procedure is cubital tunnel decompression involving the slitting the F.C.U aponeurosis. It is surgically simple and as anatomical course of the nerve is not altered; early rehabilitation can be started after the procedure. But if compression is in the retrocondylar groove and not the cubital tunnel then ulnar nerve decompression is not the procedure of choice. Anterior transposition of the ulnar nerve involves slitting the aponeurosis, mobilizing it anteriorly and embedding it in subcutaneous or intramuscular or sub muscular plane. Subcutaneous placement is associated with maximum failure rate. Poor technique, damage to the vasa nervosum and scar formation causing delayed compression are said to be the cause for complications like persistent paraesthesias. Medial epicondylectomy and slackening of the entrance and roof of the cubital tunnel are also performed to treat U.N.E. Medial epicondylectomy has limited surgical dissection and limited nerve mobilization is associated with less risk of nerve damage. The literature analysis by Bartels et al shows that simple decompression and submuscular transposition have best results. Medial epicondylectomy and subcutaneous/intramuscular transposition had worst outcomes (83,84). A meta analysis of various randomized controlled trials comparing simple decompression and anterior transposition showed that both surgeries were equally effective regardless of the severity and duration of U.N.E. No statistical significance was found between the two procedures but anterior transposition was associated with better outcome (85). Many studies were done where

intraoperatively it was found that ulnar nerve compression in cubital tunnel occurs only in 25% of cases, and yet it is puzzling to find that cubital tunnel decompression has been shown to be effective for most of the patients. But theoretically compressions at sites other than cubital tunnel cannot benefit from decompression surgery. Intraoperative electrophysiological testing to aid the surgeons in localizing the lesion can help in making a decision between decompression or transposition surgeries (74).

5) Ulnar Neuropathy at Elbow in Hemophilia.

Peripheral neuropathies are seen commonly in people with hemophilia. The common cause for peripheral nerve involvement is external compression of the nerve by haematoma/haemarthrosis. Bleeding induced compartment syndrome, intraneural bleeding and chronic entrapment neuropathy are less common mechanisms by which nerves get damaged in haemophilia. Prevalence of peripheral neuropthies in haemophilia has been reported to be 4 to 19% (11,16). Most commonly reported peripheral neuropathy has been the femoral neuropathy following a psoas bleed, followed by ulnar and median neuropathies (12).

The elbow is the most common site of haemophilic arthropathy in upper limb. It is due to the large amount of synovium in diarthrodial hinge joint making it vulnerable to repeated haemarthrosis. Recurrent intra articular bleeds triggers synovial hypertrophy. Chronic hypertrophic synovitis of the joint in turn causes destructive changes and end-stage haemophilic arthropathy. Joint contractures result when the synovium is replaced by dense scar tissue. Restriction of joint motion especially extension is seen in haemophilic elbow arthropathy (86). Goddard describes 3 main types of elbow joint involvement in haemophilic elbow arthropathy namely medial arthropathy, lateral arthropathy and global arthropathy. The ulnar nerve entrapment has been opined to occur more with medial arthropathy in different studies (41,54). Some studies have observed that ulnar neuropathy is associated more with global arthropathy of the elbow joint (2). Many studies and case reports describe ulnar neuropathy in people with haemophilia but only few of them describe U.N.E (8,9,11,16).

The literature regarding U.N.E is scarce despite haemophilic elbow arthropathy being a commonly prevalent condition in haemophiliacs. The reasons for it could be that the problems due to ulnar nerve compression which doesn’t affect their overall upper limb functioning may be overshadowed by many other musculoskeletal problems which warrant urgent treatment. Hence the

patients with haemophilia do not frequently present with specific complaints of ulnar neuropathy. Even on presenting with the complaints, the muscle wasting, reflex disturbances and sensorimotor symptoms are usually attributed to hemophilic arthropathy, immobilization and disuse related conditions by the treating physicians. Subclinical involvement of the ulnar nerve may form a majority of cases while those presenting with symptoms might be just representing the tip of the iceberg. Needle EMG studies are avoided in haemophilia patients due to risk of bleeding and all nerve pathologies may not be detected only by nerve conduction studies with surface recordings. The study done by Mortazavi et al reported a case series of six haemophilia patients with U.N.E where the results of subcutaneous anterior transposition of ulnar nerves were reported. The study has limitations in having a few subjects and being a retrospective study spanning over 20 years with a very heterogenous data. U.N.E is a common cause and has to be considered while evaluating hand disability in patients with haemophilia.

3. Methods

Setting:

Christian Medical College hospital (CMCH) is a tertiary care hospital situated in Vellore, Tamil Nadu, India, with an inpatient capacity of approximately 2500 beds, and average outpatient attendance of about 5000 persons per day. The Department of Physical Medicine & Rehabilitation in CMCH has an average outpatient attendance of about 100 persons per day and has a total inpatient capacity of about 120 beds. Every year, about 220 persons with haemophilia, predominantly from Kerala, Tamil Nadu, Andhra Pradesh, West Bengal, Karnataka, Bihar and Jharkhand, are referred here for rehabilitation following musculoskeletal complications. The services provided for them include neurological, musculoskeletal, occupational therapy evaluation and intervention such as structured physical therapy, ADL training, corrective serial casting, manipulation under anaesthesia and Yttrium synovectomy done on outpatient and inpatient basis. The electrophysiology laboratory facility of the department routinely does EMG/NCV studies to diagnose plexopathies and peripheral nerve lesions.

The study:

The study was approved by the Institutional Review Board of the Christian Medical College. The study was conducted between October 2011 and December 2012. During this period about 200 patients attended the multispecialty haemophilia clinic and therapy as outpatients in department of PMR for various musculoskeletal problems. They were approached and were informed about the study. The nature of the study, its necessity, the procedure, likely and unlikely complications arising from the study was explained to them. Among them, 50 consecutive individuals who consented for the study and met the

inclusion and exclusion criteria were recruited for the study, after obtaining an informed consent from them or from their guardians.

The patients were recruited according to following inclusion and exclusion criteria:

Inclusion Criteria:

1. Diagnosed patients of Haemophilia A with factor VIII levels below 30 % and Hemophilia B patients with factor IX levels below 30 % of normal.
2. Able to give informed consent or in case of children below 18 years should be accompanied by guardian who is able to give consent.
3. Age above 3 years.

Exclusion Criteria:

1. Active joint bleed in elbow and/or synovitis and/or myositis where extent of inflammation can affect the recording of Ulnar NCV.
2. Fever at the time of recruiting for the study or when measuring ulnar nerve conduction.
3. Patients diagnosed with neuromuscular and/or rheumatologic disorder affecting the elbow joint, hand muscles and ulnar nerve were excluded.
4. Patients with complications requiring immediate intervention like acute pseudotumors, severe acute visceral, intracranial or intravitreal bleed at the time of selection were excluded.

Data regarding the type of haemophilia, factor levels, severity of the disease, inhibitor status was collected. Personal history including their age, education, occupation, dexterity and history of any change of dexterity was collected.

The current joints in which frequent bleeding was present was documented and those joints with a bleed frequency of more than 3 bleeds in the past 6 months was documented as "Target Joint". The history of bleeding frequency in right and left elbows, past history of any fractures, surgeries or procedures around the elbow was collected.

All the patients were enquired about the symptoms of U.N.E. The symptoms of pain, paraesthesias, numbness along the medial elbow, medial aspect of forearm, and medial one and half digits and ulnar border of hand and weakening of hand grip were documented. History of whether they were experiencing the symptoms now, if they had experienced them within last 3 months, or more than 3 months ago or never had the above symptoms was documented. The history of severity of symptoms was documented as well as whether or not they were interfering with their daily activities or with some specific activities like writing/ typing and if they worsened with sleep or with activities involving prolonged elbow flexion. The habitual patterns of leaning over the elbows, supporting the head while reading or watching television in sitting or lying position and sleeping with flexed elbows were also noted. The history was asked in the language understood by the patients or/and their guardians. Pictures were used when asking about sensory symptoms in the ulnar nerve distribution area.

Examination included physical examination of the joints. Measurement of the flexion/ extension ranges of the elbow joints and range of pronation and supination in the forearms using a standard goniometer was done following the standard principles of goniometry.

The stage of haemophilic arthropathy of each elbow joint was documented after examination and history. If there was no sign of joint bleed or inflammation in the elbow and if the joint had normal range of motion, it was documented as a normal joint. The joint was documented to be in acute haemarthrosis if history of acute bleed in the joint was present with the patient having the "aura" of bleed and/or if tense swelling of the joint with pain, tenderness and warmth was seen. If a soft to firm synovial thickening on gentle palpation was noted with obscured bony land marks around the elbow joint, the joint was termed

to be in chronic synovitis stage. If mild to moderate restriction of range of motion (<50%), joint crepitus and radiographic changes as partial reduction in joint space was seen, the joint was documented to be in early arthritis and if the joint had severe ROM restriction (>50%), if the crepitus was felt when the joint was moved and the radiographs showed severe joint space reduction, the joint was documented as end arthritis.

The radiographs of bilateral elbow joints taken for evaluating the elbow bleeds as a part of management of elbow bleeds were analyzed and classified based on joint space reduction, sclerosis of subchondral bone, juxta articular osteoporotic changes found in 3 different areas. The involvement of predominantly radio humeral or lateral joint, predominantly ulno humeral or medial joint or the global joint involvement was documented.

The Ulnar nerve examination included provocation tests for U.N.E, sensory examination and motor examinations to detect ulnar neuropathy. The sensation of fine touch was detected by checking if patient could perceive and indicate the touch with a 10 gram monofilament, when he was touched in the pulp space of little finger and ulnar border over dorsum of hand with a pressure just enough to slightly bend the filament. The sensation perception when preserved was compared with the sensation over the first web space of the hand and noted if reduced sensation was present in comparison was noted. The 2 point discrimination distance was checked with a 2 point discriminator over the pulp space of little finger and the ulnar border of dorsum of hand. If the minimum distance of perception of two discrete touch sensations as two sensations was more than 5 mm, it was considered abnormal.

The motor examination included testing for signs of motor weakness in ulnar innervated muscles by performing Froment's test, looking for Wartenberg's sign and checking for wasting of FDI muscle in both the hands. Froment's test was done by asking the patient to grip a piece of paper with his lateral pinch between opposing surfaces of thumb and the lateral border of index finger, with wrist in slight flexion. The Froment's sign was considered positive if flexion of the IP joint of the thumb was noted

while performing the action. The Wartenberg's sign was said to be positive when inability to fully adduct the extended little finger with wrist in neutral and forearm fully pronated was noted. The wasting of FDI was checked for in bilateral upper limbs by inspection and palpation over the dorsal aspect of first web space.

The Elbow Flexion provocation (E.F) test involves putting elbow in 90 degrees or at maximum flexion for 60 seconds. Presence or worsening of paraesthesia/numbness in ulnar distribution indicated and was documented as U.N.E. The Tinel's sign was examined by gently tapping the nerve along the course of ulnar nerve around the elbow joint and the patient was asked to report if any paraesthesias in ulnar nerve distributed area was present.

Diagnosis of UNE by ulnar nerve NCV study: The subjects satisfying the inclusion and exclusion criteria underwent NCV study of ulnar nerve in bilateral upper extremities. The measurements were done using *Medelec Synergy multichannel EP and EMG systems manufactured by GE (VIASYS) health care* (Figure 3.1). All measurements were done in a standard setting in the EMG lab in the Department of PMR, CMC Vellore.

The room temperature was maintained in a constant range. Skin temperature around both the elbow joints was measured and it was maintained between 34-37 degrees Celcius, any abnormality in temperature was documented. All the elbows were kept at a constant 90 degrees of flexion (with full extension of elbow being considered 0 degrees) during all stimulations and recordings. If a contracture or deformity of the joint prevented the elbow flexion to 90 degrees, the angle at which recording was done was noted and it was ensured that stimulation and recording were done at same elbow position. The process of recording NCV was as follows:

After the initial explanation of procedure to the patient and positioning of the patient, the following electrodes were placed:

Recording electrode (R) – a surface electrode placed on Abductor Digiti Minimi (ADM) and later over First Dorsal Interossei (FDI) muscle belly. Recording electrodes for recording SNAPs were the ring electrodes placed over the little finger.

Ground electrode (G) a surface electrode placed on a neutral point between the stimulation and Recording electrodes.

Stimulating electrode (S) – stimulus was given at fixed points at wrist (3 cms proximal to distal crease), distal to elbow (3-4 cms distal to medial epicondyle) and proximal to elbow (5-8 cms proximal to medial epicondyle) and in the axilla along the course of the ulnar nerve on the lateral wall of axilla with a surface stimulator. Care was taken to maintain the minimum distance of 10 cms between stimulation points around the elbow to minimize error. However, in some cases, swelling and distortion of local anatomy around the elbow joints prevented getting a normal wave pattern from the point meant for below elbow stimulation. In such cases, the stimulation was given along the course of ulnar nerve more distally, deep in the belly of F.C.U.

Fig 3.1: *Medelec Synergy multichannel EP and EMG systems*

Electrophysiological findings suggestive of U.N.E in the nerve fascicle supplying the particular muscle or sensory supply were: Ulnar nerve NCV falling below 50m/s in across the elbow segment, slowing of

NCV by more than 10m/s in the AE-BE segment in comparison to NCV from BE-Wrist segment, a drop of CMAP amplitude across elbow by more than 50% or area reduction of more than 40% with dispersion.

UNE was considered to be present in the upper limb when:

1. Symptoms or clinical signs of UNE were present with any one of the impairments in the NCS of ulnar nerve recorded from ADM, FDI or SNAP from the fifth digit.
2. No signs or symptoms were present on clinical examination, but consistent abnormality was seen in at least two out of three NCS in each upper limb.

The prevalence of U.N.E was calculated in terms of number of persons per 100 people with haemophilia.

4. Statistical methods:

Descriptive statistics - mean, standard deviation and range were done for continuous data. Univariate analysis of the variables from data regarding the bleeding frequency of the joint, stage of haemophilic arthropathy of each joint and radiological classification of the joint was done to evaluate their association with U.N.E using Chi-square test and Chi- square for trend test (as they all were categorical variables). For this study, *p value* less than 0.05 was considered as significant. To reduce the errors during data entry, *Epidata* software was used. The Chi square test and Chi square for trend tests were performed using the software *EpiInfo*. Both *Epidata* and *EpiInfo* are free to use software recognized and officially used by the W.H.O.

5. RESULTS

A total of 50 patients were recruited in the study. Detailed history was recorded, and all of them underwent clinical examination for signs of U.N.E and ulnar nerve conduction studies in bilateral upper limbs.

Socio - Demographic profile of the study population:

50 individuals with haemophilia satisfying the inclusion and exclusion criteria participated in the study and completed the study. There were no dropouts from the study.

Age: The age of the oldest patient was 44 years and that of the youngest was 6 years. The median age of all patients in the group was 17.7 years (Figure 5.1).

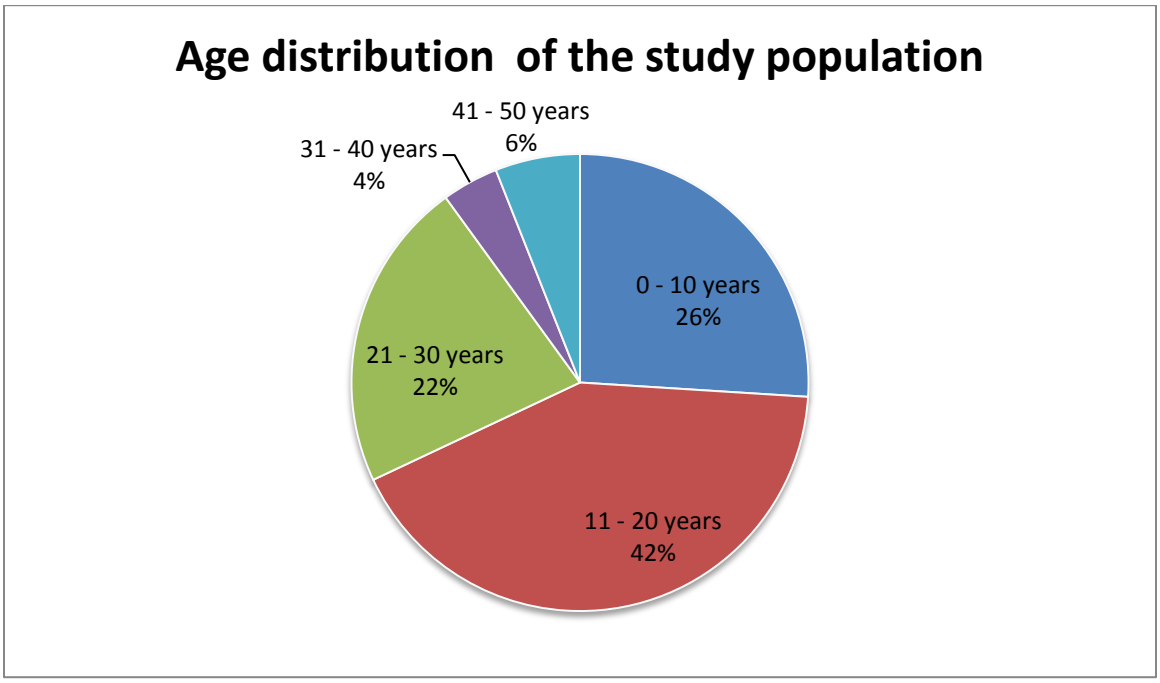


Fig 5.1: Age distribution of the study population.

Geographical distribution of the patients:

Out of 50 patients, 20 were from Kerala, 12 were from Tamil Nadu, 8 were from West Bengal, 3 patients were from Karnataka, 2 patients were from Andhra Pradesh, 1 each from the states of Bihar, Jharkhand, Tripura, Assam and 1 patient from Bangladesh (Figure 5.2).

Figure 5.2 The geographical distribution of study population.

Education: 12 patients were studying in or had studied less than class 5, 28 patients were studying in or had studied from class 5 to class 12. 7 were studying or had completed their graduation and 3 patients had a post graduate degree.

Vocation: 38 patients were students, 11 were engaged in skilled activities and desk jobs and 1 patient was currently unemployed.

Type of haemophilia:

42 patients had haemophilia A and 8 had haemophilia B. Among them 1 had mild haemophilia (Factor level 5%-30%), while 2 participants had moderate haemophilia (Factor level 1% - 5%) and 47 patients had severe haemophilia (Factor level <1%).

Bleeding frequency in the elbow joint and U.N.E:

Among the 100 elbow joints examined, 24 joints were target joints with bleed frequency more than 3 times in 6 consecutive months, 41 joints had bleeding episodes had history of bleeds less than 3 episodes in 6 months and 35 elbow joints had no bleeding episodes ever (Fig 5.3).

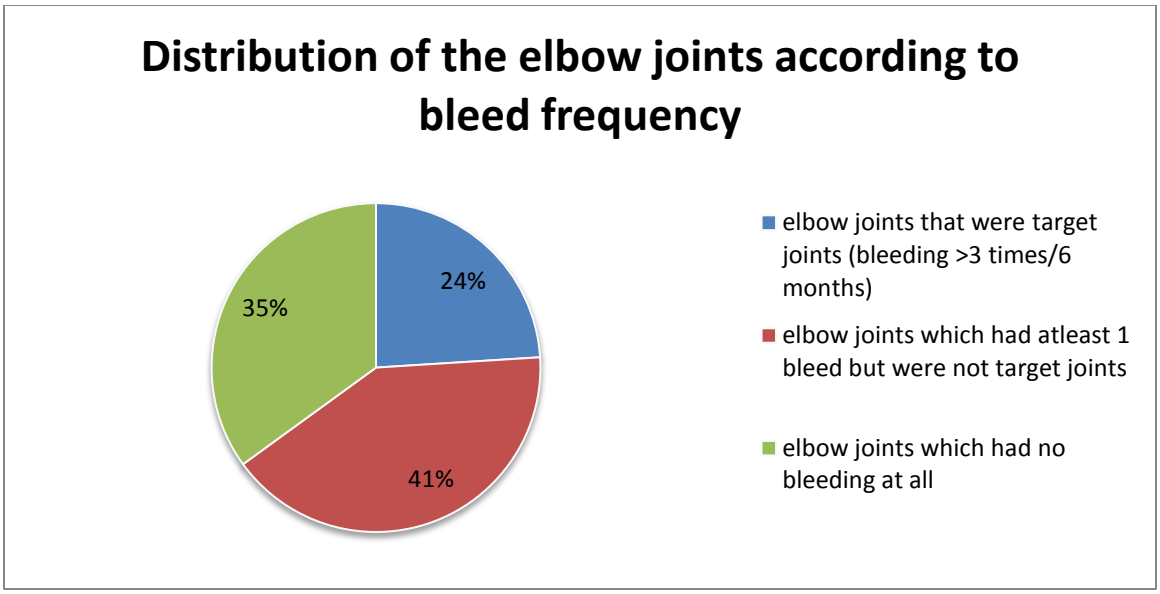


Fig 5.3: Distribution of the elbow joints according to the bleed frequency.

The Chi-square test was applied to find the association between 24 elbows which were target joints for frequent bleeding and U.N.E. (Table 5.1)

	UNE present	UNE absent
Target joint – yes	14	10
Target joint – no	12	64

Table 5.1: Chi-square test for association between U.N.E and the elbow being a target joint

The relative risk of a target joint being associated with U.N.E is 3.69 (Taylor series 95% CI 1.99 – 6.87) with Yate's corrected Chi square value of 18.33 and p value of 0.00001064.

Clinical symptoms of UNE:

17 patients complained of symptoms of UNE. A dull aching vague pain along the medial aspect of elbow, medial aspect of wrist and ulnar border of hand was complained by 9 patients (18%), paraesthesia in the ulnar border of hand, medial one and half fingers and medial aspect of wrist was seen in 4 patients (8%) and 2 patients each (4%) had complaints of numbness and weakness of hand grip (Figure 5.4).

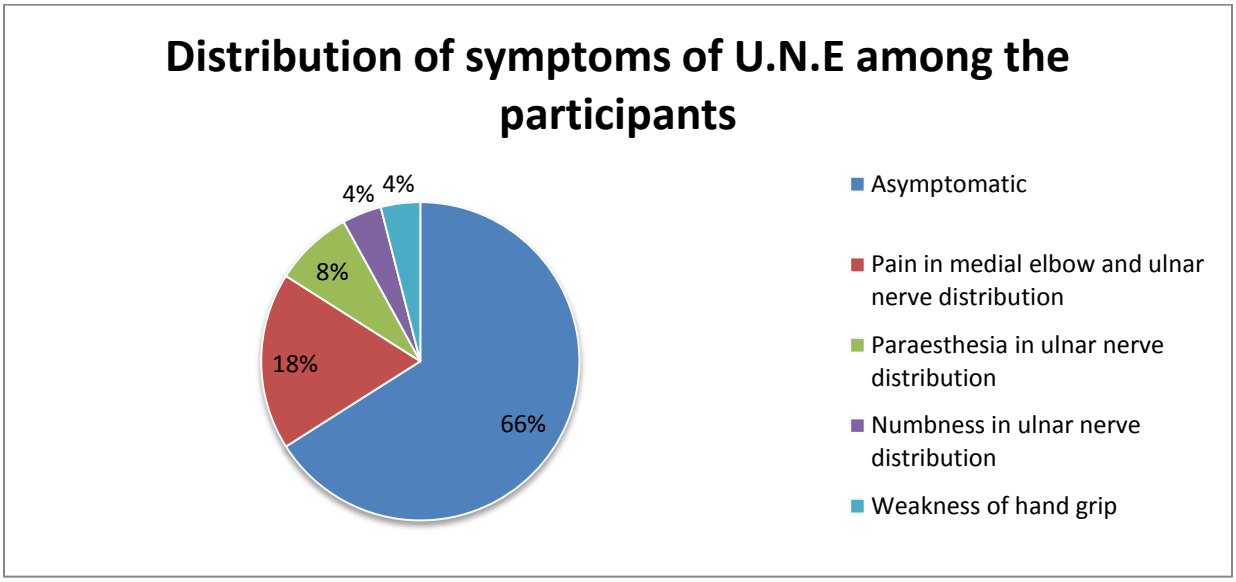


Fig 5.4: **Distribution of symptoms of U.N.E among the participants**

Among the 17 patients who had symptoms, 11 (22%) were experiencing the symptoms currently, 4 had experienced one of the symptoms less than 3 months ago, and 2 patients had experienced one of the symptoms in the past more than 3 months ago (Figure 5.5).

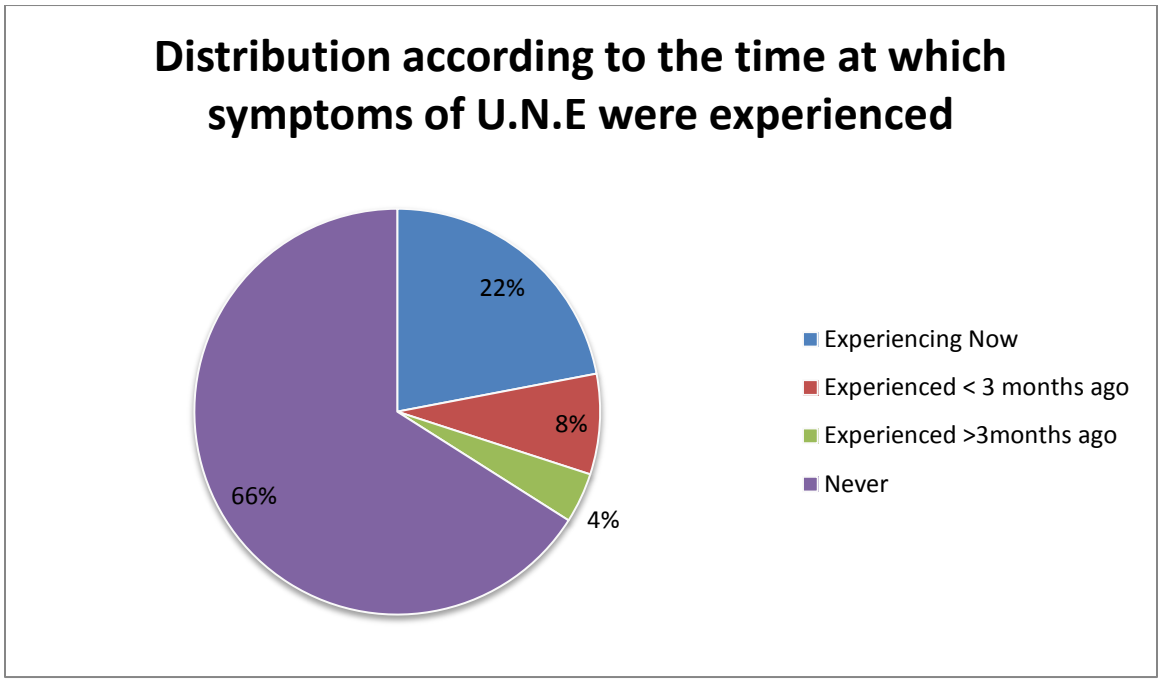


Fig 5.5: Distribution of the patients according to the time at which symptoms of U.N.E were experienced

The severity of symptoms also varied among the symptomatic patients. 8(16%) patients said the symptoms didn't interfere with their activities. 4 patients (8%) had symptoms which interfered with some activities like writing or speaking over cell phone or using elbow crutch etc. 5 patients had severe symptoms which were more troublesome at night and/or prevented them from performing any activity which required prolonged flexion (Figure 5.6).

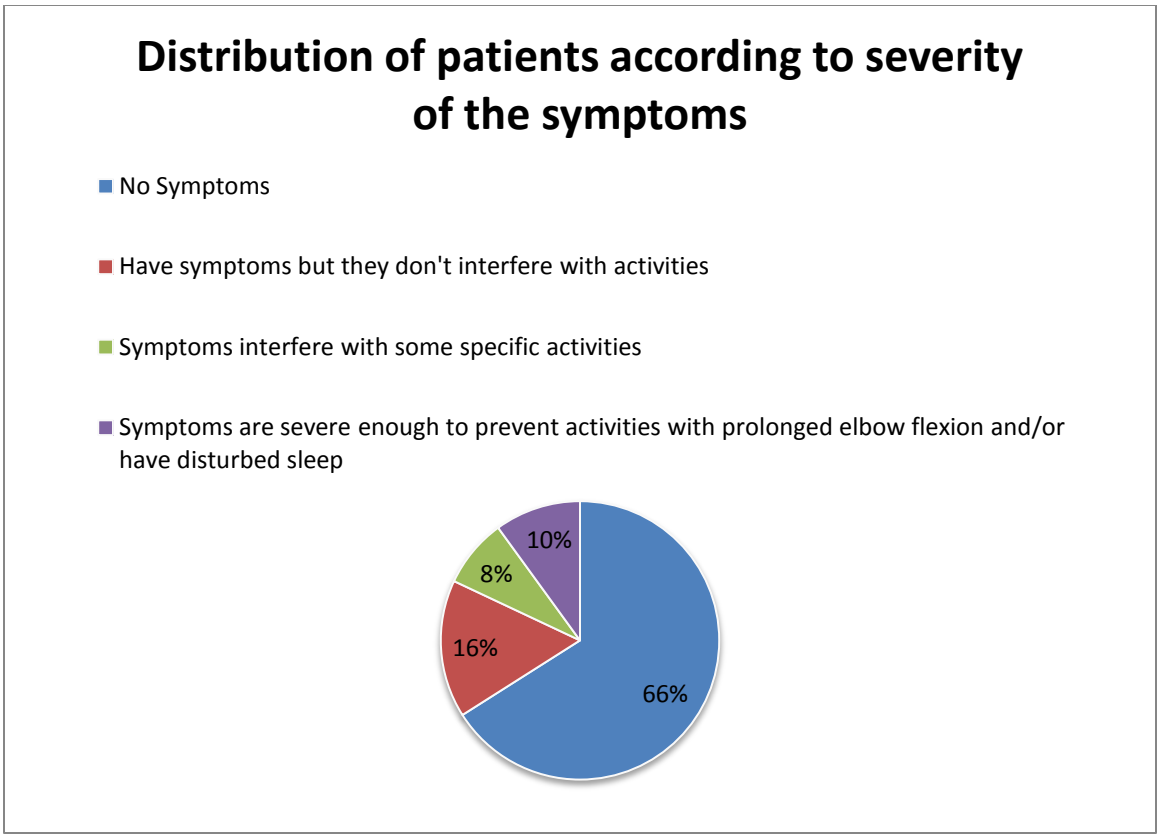


Fig 5.6: **Distribution of patients according to severity of the symptoms**

Clinical signs of U.N.E:

All the patients with symptoms of U.N.E and 2 patients without any history of symptoms of U.N.E were found to have at least one of the clinical signs tested to be positive. Of 100 upper limbs examined for ulnar nerve impairment the sensory impairment on testing for pressure using 10 grams monofilament was found in 9 (9%) upper limbs. 2 point discrimination was found to be impaired in 6(6%) upper limbs. The 60 Second Elbow Flexion Provocation test was found to be positive in 5 (5%) upper limbs. Tinel's sign was positive in 17(17%) upper limbs. The motor signs tested were Froment's test, Wartenberg's sign and wasting of FDI muscle. The Froment's test was found to be positive in 12 (12%) upper limbs, Wartenberg's sign was found in 2 (2%) upper limbs and wasting of FDI was seen in 17(17%) upper limbs (Figure 5.7, 5.8, 5.9).

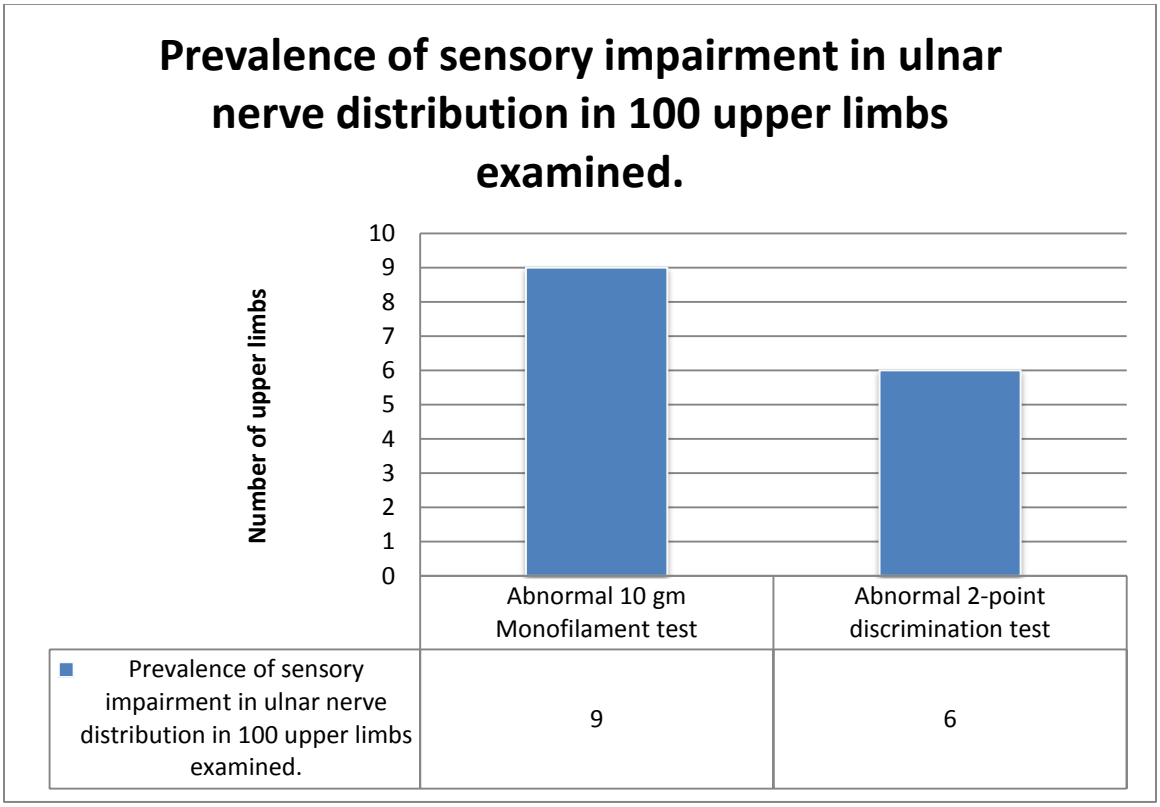


Fig 5.7: Prevalence of sensory impairment in ulnar nerve distribution in study population.

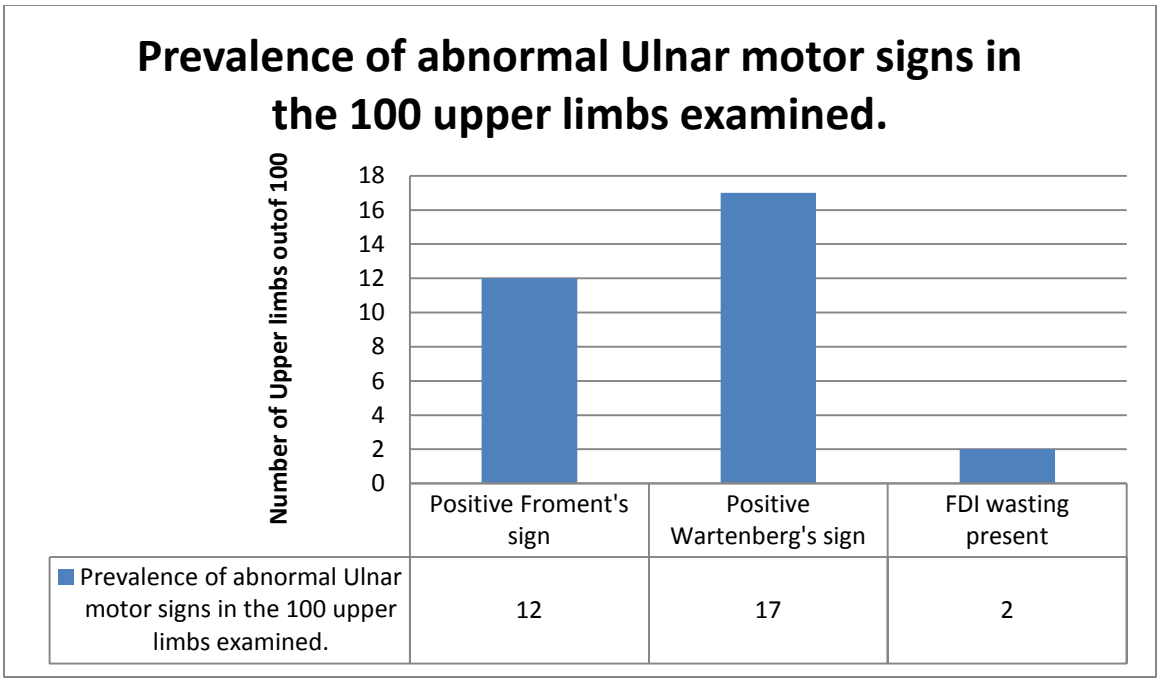


Fig 5.8: **Prevalence of abnormal ulnar motor signs in the study population.**

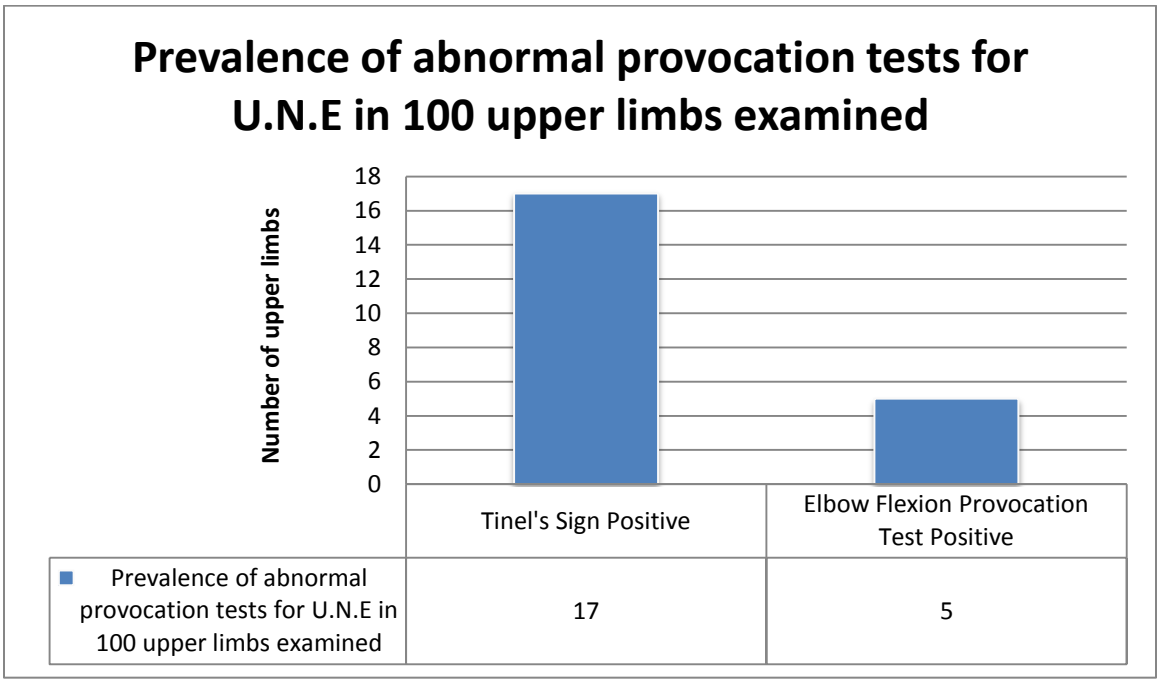


Fig 5.9: **Prevalence of abnormal provocation tests for U.N.E in 100 upper limbs examined**

Results of Ulnar Nerve Electrophysiological study:

All 50 participants underwent NCS of ulnar nerves in both the upper limbs. In each upper limb ulnar nerve CMAPs were recorded from ADM and FDI muscles and SNAPs were recorded from digit V. The CMAPs from ADM and FDI were assessed for any drop in nerve conduction velocity (absolute value <50m/s and/or drop in NCS by more than 10m/s) and/or drop in amplitude (> 50% drop in amplitude or area reduction > 40% with dispersion) in the segment of the ulnar nerve across the elbow. The drop in nerve conduction velocity denotes demyelination, while drop in amplitude of CMAP denotes axonopathy secondary to compression of the ulnar nerve. Of the 100 ADM CMAPs examined, 23 showed demyelination with 7 among them showing axonopathy along with demyelination. Of the 100 CMAPs from FDI recorded, 24 showed demyelination and among them 8 had both demyelination and axonopathy. SNAPs from 100 ulnar nerves were assessed only for drop in nerve conduction velocity and 11 out of 100 ulnar nerve SNAPs showed demyelination.

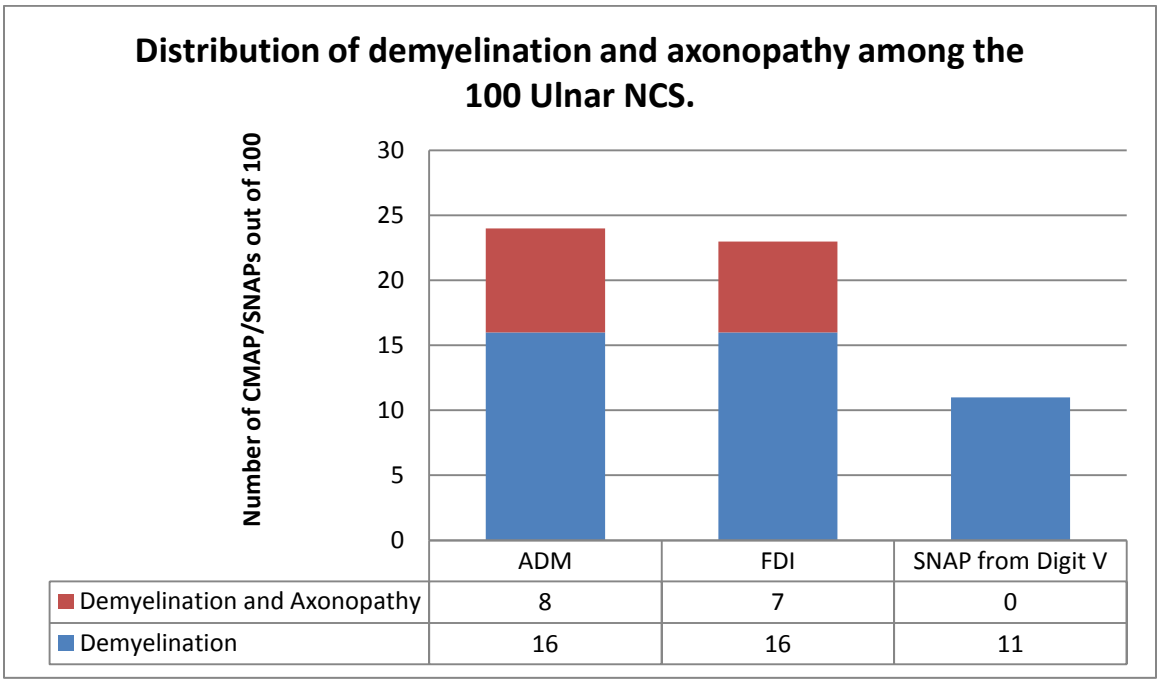


Fig 5.10: Distribution of demyelination and axonopathy among the 100 ulnar nerve conduction studies

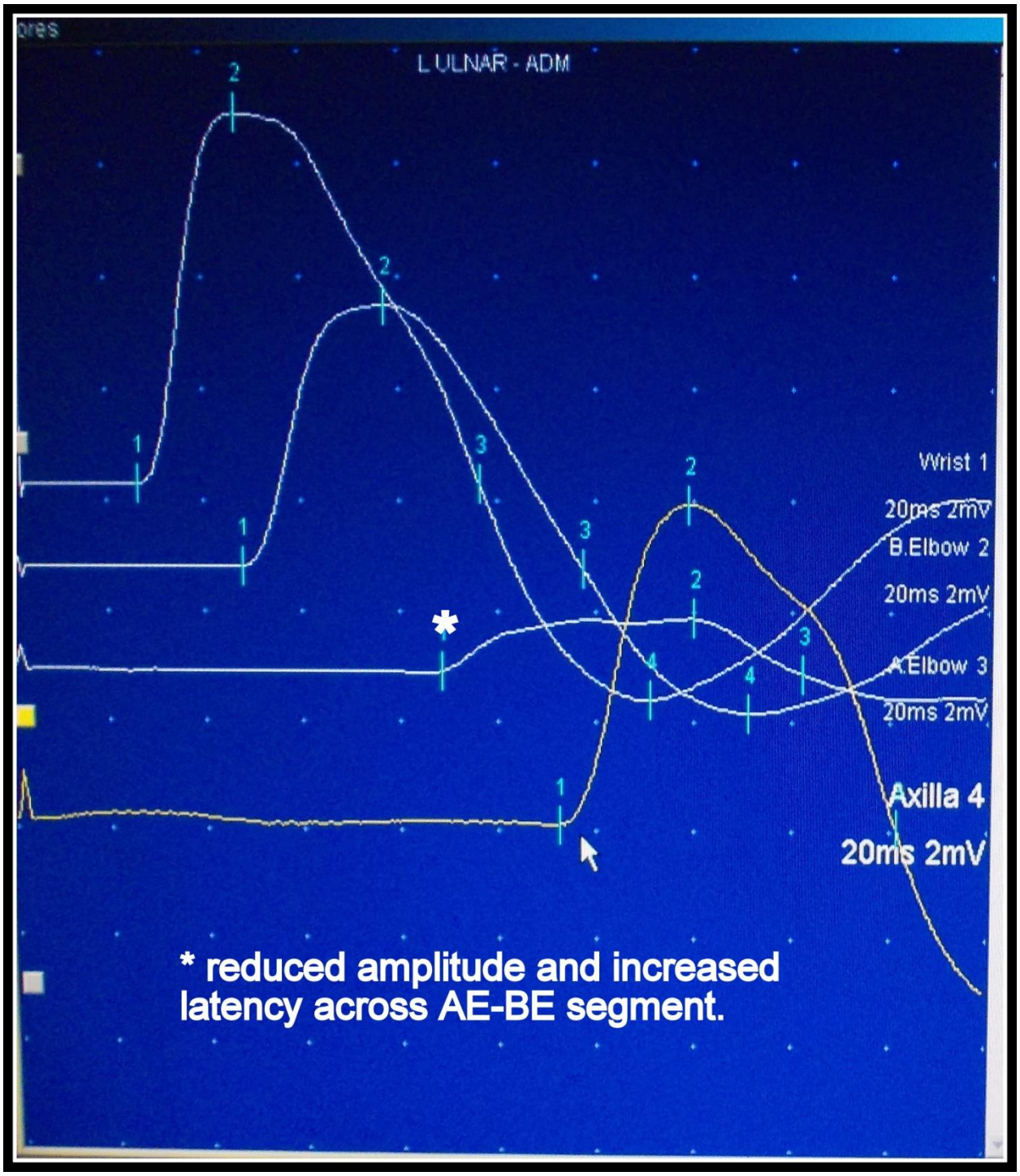


Fig 5.11: Ulnar nerve recording from the Left ADM showing prolonged latency period and significant drop in amplitude in the ulnar nerve segment across the elbow joint suggestive of both demyelination and axonopathy

Prevalence of U.N.E:

U.N.E was found in 21 out of the 50 participants (42%). The prevalence of U.N.E in the haemophilia population attending the multispecialty clinic at CMC, Vellore was calculated to be 42 per hundred people with haemophilia. Bilateral U.N.E was found in 5 individuals. Out of 100 ulnar nerves tested, 26 ulnar nerves were affected by U.N.E.

Of the 21 patients with U.N.E, 2 (4%) had subclinical U.N.E, with no symptoms or signs on clinical examination but with intrinsically consistent abnormalities seen on NCV. 2 patients (4%) did not report any symptoms of U.N.E but on examination, they showed clinical signs of ulnar nerve involvement and NCS showed changes consistent with U.N.E. Rest of the 17 patients (34%) had clinical symptoms, clinical signs and electrophysiological signs of UNE. All the patients with symptoms and signs of U.N.E had abnormal NCS (Figure 5.12 and 5.13).

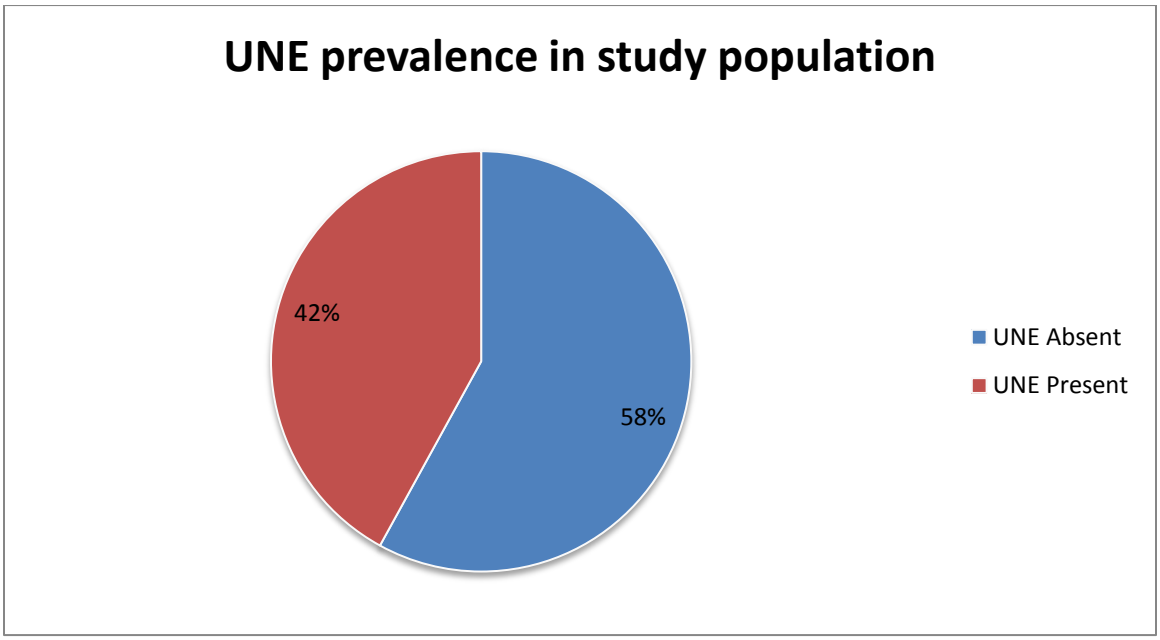
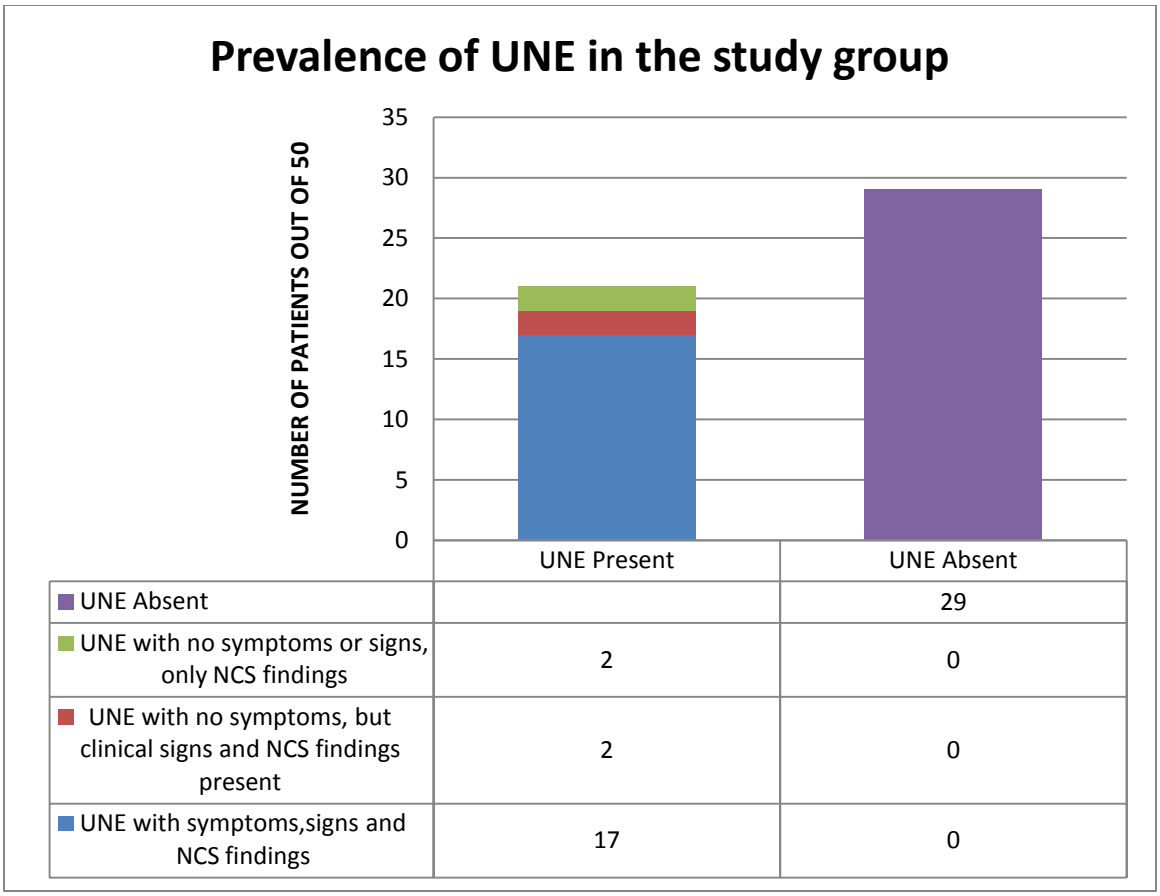


Fig 5.12: Prevalence of U.N.E in the study population.



	UNE Present	UNE Absent
UNE Absent		29
UNE with no symptoms or signs, only NCS findings	2	0
UNE with no symptoms, but clinical signs and NCS findings present	2	0
UNE with symptoms,signs and NCS findings	17	0

Fig 5.13: Prevalence of U.N.E in 50 patients of haemophilia participating in the study.

Habitual patterns of the patients and UNE:

Of the 50 patients who were examined, a history of presence or absence of habits which put the elbow at risk of developing U.N.E was also obtained. The history was obtained from the subjects and in case of the children, from the guardians accompanying them. They were asked if they felt that the subject had in their opinion, habits of leaning over the elbow while reading, watching television or while doing other tasks and/or keeping the elbow in flexed position while sleeping, more than normal (Figure 5.14). Pictures were shown of people performing such activity for better understanding of the patients/ caregivers.

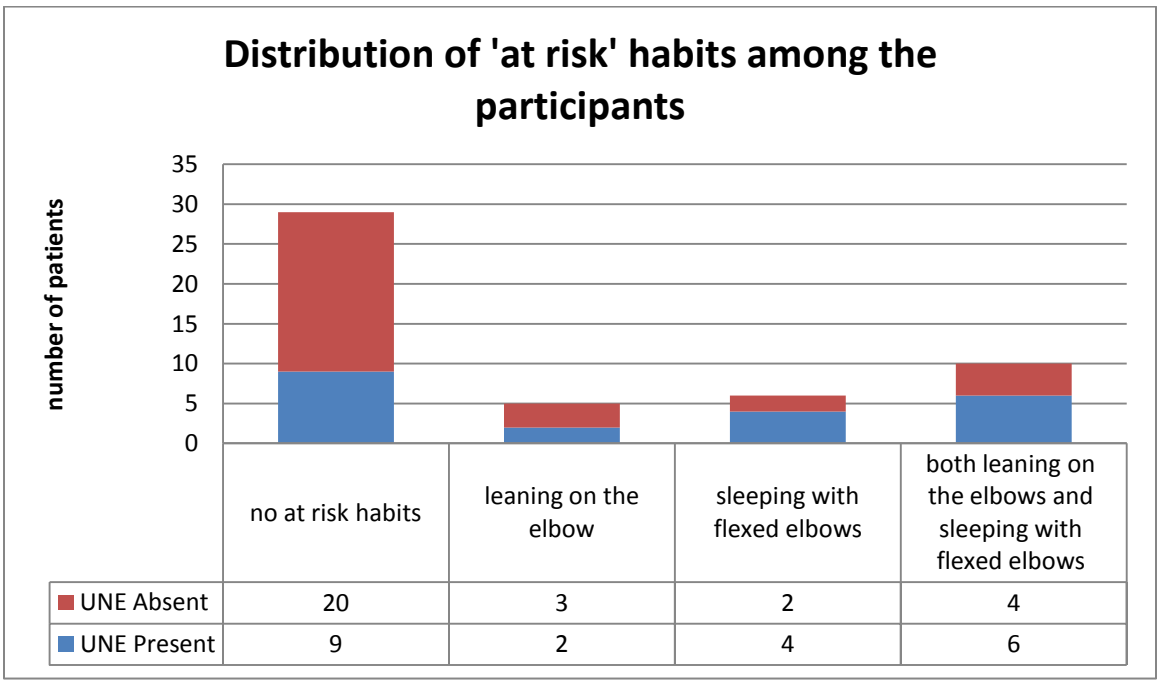


Fig 5.14: Distribution of 'at risk' habits among the participants

Out of the 50 participants, 29 of the participants gave a history of not having any "at risk" habits. 5 patients had habits of leaning over the elbow while doing work, 6 patients had habit of sleeping with their elbows flexed and 10 patients had both the habits mentioned above.

A Chi-Square for trend test was applied to find the association between the presence of "at risk" habits and UNE. The test had a p-value of 0.05 and a Chi-Square for trend value of 7.8 (Table 5.2).

	U.N.E Present	U.N.E Absent	Odds ratio
No "at risk" habits	9	20	1.00
Leaning over the elbow	2	3	1.4
Sleeping with a flexed elbow	4	2	4.4
Both leaning and sleeping with flexed elbow	6	4	3.3
Total	21	29	p- value = 0.05

Table 5.2: Chi Square test for association between "at risk habits" and U.N.E

Stage of haemophilic arthropathy of the elbow and U.N.E:

Among the hundred elbow joints examined, none of them were in acute haemarthrosis (acute bleeds were excluded), 14 elbows were found to be in the stage of chronic synovitis, 14 elbows were in the stage of early arthritis and 16 elbows were in the stage of end arthritis, while 56 joints were normal (Figure 5.15). The association between stage of haemophilic arthropathy and U.N.E was tested using Chi-Square for trend test. The P-value obtained was 0.00009 and Chi- Square for linear trend is 15.42 (Table 5.3).

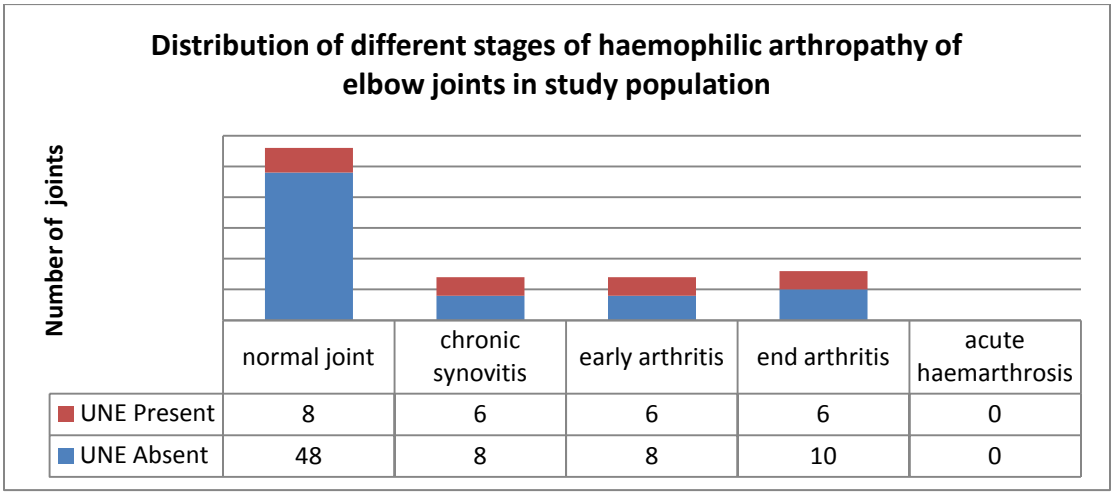


Fig 5.15: Distribution of elbow joints according to the stage of haemophilic arthropathy

	U.N.E present	U.N.E Absent	Odds ratio
Normal joint	8	48	0.22
Acute Haemarthrosis	0	0	_
Chronic Synovitis	6	8	1.00
Early arthritis	6	8	1.00
End arthritis	6	10	0.86
Total 100	26	74	

Table 5.3: Association between stage of haemophilic arthropathy and U.N.E

The Radiological joint involvement and U.N.E:

Of 100 joints examined, X rays taken as a part of treatment of elbow bleeds were used. If recent X-rays were not present or if the patient had UNE and he did not have any X-rays done, fresh X-rays were obtained. Elbow joints were considered to be normal if there was no history of elbow bleeds, if they were asymptomatic for U.N.E and had normal ulnar nerve conduction studies. Out of 100 elbow joints examined, 66 joints were normal radiologically, 2 joints showed arthritic changes in radio humeral or lateral joint, 9 joints showed arthritic changes in the ulnohumeral joint or the medial joint and 23 joints showed global arthritis (Figure 5.16, 5.17, 5.18,5.19,5.20 and5.21).

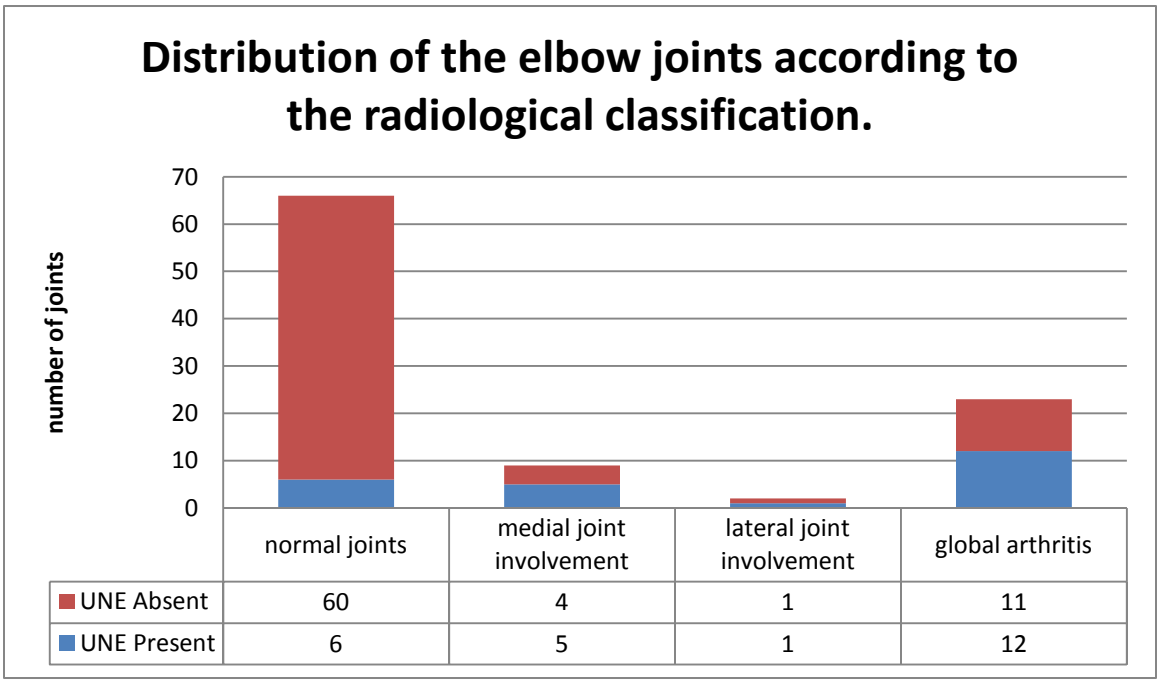


Fig 5.16: Distribution of U.N.E based on the radiological classification of the elbow joints.

The association between radiological joint involvement and U.N.E was tested using Chi-Square for trend. The test had a p-value of 0.0212 and Chi-Square value for linear trend of 5.30.

	UNE present	UNE absent	Odds Ratio
Normal joint (66)	9	57	0.17
Lateral joint involvement (2)	1	1	1.00
Medial joint involvement (9)	5	4	1.36
Global arthritis (23)	11	12	1.00
Total 100	26	74	

Table 5.4: Chi-square test for association of Radiological joint involvement and U.N.E

Fig 5.17: Plain X-ray of a normal Elbow joint AP/Lateral view

Fig 5.18: Plain X-ray of an Elbow joint showing global arthritis

Fig 5.19: Plain X ray of Elbow with haemophilic arthropathy showing predominantly medial/ulno humeral joint involvement.

Fig 5.20: Plain X-ray of elbow joint with haemophilic arthropathy with predominantly radio humeral/lateral joint involvement lateral view.

Fig 5.21 Plain X-ray of elbow joint with haemophilic arthropathy with predominantly radio humeral/lateral joint involvement AP view.

6. DISCUSSION:

U.N.E was found in 42% of people with haemophilia attending the multispecialty haemophilia clinic and being treated in the Department of PMR in CMC Vellore. The findings cannot be extrapolated to whole of the haemophilia population in India as the sample represents the patients with haemophilia who were referred to and were undergoing treatment for moderate to severe musculoskeletal complications and may not represent the heterogeneous population of haemopilia in the community. Since no similar prevalence study has been done in people with haemophilia, we were unable to compare or comment on our findings.

The clinical examination for detecting U.N.E included 2 provocation tests namely the Tinel's sign which has a sensitivity of 78% and specificity of 79% and the 60 second Elbow Flexion Provocation test which has a sensitivity of 89% and specificity of 98% (74). The pressure provocation tests and combined flexion – pressure provocation tests for U.N.E were not included despite higher sensitivity and specificity as the minimal chance of precipitating a joint bleed in patients with severe haemophilia was present. The sensory examination of the ulnar nerves included examining the pressure perception with a 10 gram monofilament and checking the 2 point discrimination distance in the pulp space and the ulnar border dorsum of hand. The motor examination included Froment's test, testing for positive Wartenberg's sign and FDI wasting. The examination of power in FCU, and FDP to little finger was not included to screen for U.N.E as the literature review of previous studies on U.N.E suggested that they are least frequently involved due to the fascicular distribution of the fibers within the ulnar nerve at the elbow (75). The rationale behind including the above 3 tests was to sample the intactness of ulnar nerve supply to thenar muscle group (Adductor Policis tested by Froment's test), hypothenar muscle group (Adductor Digiti Minimi tested by Wartenberg's sign) and the interossei (checked by looking for FDI wasting). The most common clinical symptom in the study group was pain along the medial part of elbow and ulnar border of hand. The most common sensory impairment was impaired pressure sensation to 10 gram monofilament

in the area of ulnar nerve distribution (9%). Among the motor signs tested wasting of the FDI was found to be most common (17%).

Of the 100 ADM CMAPs examined, 23 showed demyelination with 7 among them showing axonopathy along with demyelination. Of the 100 CMAPs from FDI recorded, 24 showed demyelination and among them 8 had both demyelination and axonopathy. SNAPs from 100 ulnar nerves were assessed only for drop in nerve conduction velocity and 11 out of 100 ulnar nerve SNAPs showed demyelination. The more axonopathies and demyelination cases found in FDI corresponds to the fact that more number of patients who had FDI wasting. In studies on non haemophilic patients EMG from FDI to pick early signs of degeneration is frequently recommended (78).

The diagnosis of UNE was made when:

1. Symptoms or clinical signs of UNE were present with any one of the impairments in the NCS of ulnar nerve recorded in ADM, FDI or SNAPs from the fifth digit.
2. No signs or symptoms were present on clinical examination, but consistent abnormality was seen in at least two out of three NCS done in each upper limb.

The isolated abnormal NCS data not associated with clinical signs or symptoms was considered as technical error and did not suggest U.N.E. This was because, the chance of getting erroneous data was high due to swelling of the joint. Moreover there was poor delineation of anatomical landmarks with contractures and the chances of ulnar nerve subluxation with an altered course of nerve were more in haemophilic arthropathy, both factors again leading to an erroneous data. The CMAP recording obtained from stimulation of ulnar nerve to ADM, FDI and the SNAP recording by stimulating the ulnar nerve to fifth digit were recorded and were considered in parallel, which increased the sensitivity of electrophysiological study in detecting U.N.E.

Two patients were diagnosed with subclinical U.N.E. The risk factor in one individual was use of elbow crutch on the affected elbow to aid in ambulation following knee bleed and the other individual had history of supracondylar fracture of humerus with flexion contracture of the elbow joint.

The study population included many children in their first and second decades (68% of the study population). The age distribution is consistent with the finding that children and adolescents due to the nature of their activities and changes in joints and bones associated with growth have more risk of bleeding and secondary complications such as contractures.

The geographical distribution of haemophilia in our study showed clustering of cases from northern Kerala. None of the patients who participated in our study were on primary or secondary prophylaxis for joint bleeds.

42 patients had haemophilia A and 8 patients had haemophilia B. The ratio of haemophilia A to haemophilia B was reported to be 4.2:1 in an epidemiological study (n = 2192) done in Maharashtra (87). Our study population has haemophilia A to haemophilia B ratio of 5.2:1, even though the sample size was significantly smaller in comparison.

47 patients had severe haemophilia A, 2 patients had moderate haemophilia and 1 patient had mild haemophilia. The 1 patient with mild haemophilia had come for management of frequent pain following a post traumatic gastrosoleus muscle bleed and subsequent tendoacheilles tightness. One of the patients with moderate haemophilia had come for management of flexion contracture in the elbow joint following a supracondylar fracture of the right humerus. He also complained of recurrent swelling around his left elbow (about once a month) but with no history of elbow bleeds. He did not have any symptoms or signs of U.N.E, but bilateral ulnar nerve conduction studies showed consistent changes in CMAP from ADM and FDI. The second patient with moderate haemophilia was a 42 year old gentleman, who presented with complaints of bilateral knee pain after walking long distances and was found to have bilateral osteoarthritis on evaluation. The patients with mild and moderate haemophilia bleed less frequently than

the patients with severe haemophilia and carry a much lesser chance of developing haemophilic arthropathy and long term musculoskeletal complications (88). The mild and moderate haemophilia patients in our study group had no history of joint bleeds and all had come for complaints unrelated to haemophilic arthropathy. The low percentage of patients with mild and moderate haemophilia can be explained by the fact that our hospital is a tertiary care centre where majority of the patients attending the multispecialty haemophilia clinic have severe haemophilia with various musculoskeletal complications.

There was history of bleeding at least once in 65 elbow joints while, 35 joints had never bled. Elbow joint has been reported as the second most common joint to bleed in haemophilia and this fact is corroborated by the high prevalence of elbow bleed in the study population(2).

The standard definition of a target joint is very ambiguous. In Canada the target joint is defined as a joint that bleeds more than 3 times in 3 consecutive months (89). The World Federation for Haemophilia in its "guidelines for management of haemophilia - 2012" defines a target joint as "a joint having more than 3 bleeding episodes in 6 consecutive months" (90).The consensus definition in WFH guidelines was considered to define target joint in our study population. The association between 24 elbows which were target joints for frequent bleeding and U.N.E was assessed by applying Chi square test. The test had a p-value of 0.00001064 and a relative risk of 3.69 (95% CI values were 1.99 and 6.87) was found in an elbow that was a target joint for U.N.E. The statistically significant p – value (< 0.05) suggests that this observation is not due to chance and the elbow which is a target joint has a 3.69 times more risk of having an associated U.N.E. The finding can be explained physiologically by the fact that recurrent haemarthrosis is associated with flexed posture of the elbow joint, which reduces the diameter of cubital tunnel leading to compression of ulnar nerve. The haemarthrosis and the associated synovial hypertrophy cause the retrocondylar groove to become shallow, making the ulnar nerve more vulnerable to external pressure. This finding also stresses on the role that timely factor replacement and prevention of developing chronic synovitis in the joint has. If the joint is already in the stage of chronic synovitis, apart from factor replacement, Yttrium synovectomy can reduce the joint bleed frequency significantly.

The association between stage of haemophilic arthropathy and U.N.E was tested using Chi-Square for trend test. The p-value was 0.00009 (<0.05) and Chi- Square for linear trend was 15.42. The odds ratio of 1.00 for stages of chronic synovitis and early arthritis, 0.8 for stage of end arthritis and 0.22 between normal joint and U.N.E was found. This indicates that there is no correlation between the stage of haemophilic arthropathy and U.N.E and the result is statistically significant. One of the exclusion criteria for recruiting the patients was the presence of acute haemarthrosis. There was no patient in the study group with a recent onset of bleed in the elbow joint or had an elbow in acute haemarthrosis stage. The patients who were detected to be in chronic synovitis stage with repeated bleeds in the elbow joint were suggested Yttrium synovectomy along with exercises and factor replacement.

Of the 100 elbow joints examined, 66 joints were normal radiologically, 2 joints showed arthritic changes in radio humeral or lateral joint, 9 joints showed arthritic changes in the ulnohumeral joint or the medial joint and 23 joints showed global arthritis. The test had a p-value of 0.0212 (<0.05) and Chi-Square value for linear trend of 5.30. The Odds ratio of 1.36 between the ulno humeral or medial joint involvement indicates that there is higher chance of developing U.N.E when the hemophilic arthropathy affects the medial joint. The p-value suggests that this finding is statistically significant. The involvement of only ulno humeral joint or only radio humeral joint is seen in early arthritis and later as the haemophilic arthropathy progresses, global arthritic changes are seen. The greater risk of ulno humeral joint involvement of developing U.N.E is mentioned in the study by Silva et al (54). However Mortazavi et al in their study found that all the cases of U.N.E in their study group were associated with global arthritis in the respective elbow joints (2). Surgical options like excision of the medial condyle of humerus or anterior ulnar nerve transposition can be tried if severe ulnar neuropathy is seen. For joints with chronic synovitis associated with enlarged radial head, excision of radial head with synovectomy has been suggested to prevent recurrent bleeds and further joint damage.

History of habits like leaning on the elbow while doing certain activities like reading or watching television and sleeping with elbows flexed was documented in all the participants. 29 patients denied

having any “at risk” habits, 5 patients had habit of leaning over their elbows, 6 patients had habit of sleeping with their elbows flexed and 10 patients had both of the above habits. The association between presence of “at risk” behavior and the U.N.E was assessed using Chi-square for trend test. The p-value of the test was 0.05 (the accepted limit is p value <0.05). Hence the association suggested by odds ratio of 1.4 between habit of leaning over elbow, 4.4 between the habit of sleeping with a flexed elbow and 3.3 of both the above habits with U.N.E, cannot be considered to be statistically significant.

All participants enrolled in the study were educated about the conditions and behavioral modifications were taught to avoid the habits which put the ulnar nerve at risk of more compression. Use of splints and elbow pads to minimize the risk of U.N.E in those with elbow in recurrent haemarthroses or chronic synovitis stage was advised. Those using elbow crutches for ambulation were taught the right method of weight transfers with elbow crutches to avoid crutch associated ulnar nerve palsy. They were advised to use elbow crutches that were custom made if ROM in the elbow was restricted and use of mobility aids and wheelchair with a good padding over armrests to prevent U.N.E.

Patients who were diagnosed with U.N.E were educated about the warning signs of increase in loss of sensation, wasting of intrinsic hand muscles and weakening of hand grip. The importance of early intervention like ulnar nerve decompression or anterior transposition of ulnar nerve to prevent further damage was stressed upon.

Special cases:

One patient had signs of ulnar neuropathy with wasting of hand muscles and sensory impairment in the palmar surface of medial one and half digits suggestive of ulnar neuropathy, but the preserved strength in FDP of little finger, F.C.U strength and intact sensation and SNAPs from dorsum of the hand indicated the ulnar neuropathy at wrist. The primary reason for him seeking medical attention was for haematoma in left gluteus maximus. During the period of acute bleed and his journey to the hospital, for a

period of 2 – 3 days he sat, lifting his left gluteal area up by bearing weight on the right upper limb. The prolonged dorsiflexion and compression of the ulnar nerve in the Guyon's canal was speculated to be the cause of ulnar neuropathy at wrist. With conservative management and timely treatment with factors, the ulnar neuropathy gradually improved.

Another boy of 17 years had a history of Subdural Haemorrhage (SDH) in the right frontoparietal region, about three months before presenting to our hospital, following trauma at his school. It was treated conservatively in an ICU at a multispecialty hospital in their city. Following the SDH, he developed weakness and wasting of the left upper limb hand muscles with flexion contracture of the elbow, and the patient was told that the left upper limb monoplegia was secondary to the right subdural haemorrhage and it was recovering. However on examination, it was clinically and electrophysiologically found that weakness was isolated to the left ulnar nerve. The left radial and median nerve CMAPs and SNAPs were intact. Significant wasting and inability to use needle EMG prevented the confirmation of the diagnosis. However the clinical picture, NCS data and history of left elbow being a frequent bleeding joint with severe flexion contracture, suggested severe U.N.E in his left upper limb. Ultrasonography of elbow showed significant compression and ill defined ulnar nerve within the retrocondylar groove and the cubital tunnel (Figure 6.1). He was referred to Department of Hand Research for further surgical management. In view of severe ulnar nerve involvement with wasting and the status of hi serum being positive for inhibitors to factor VIII, immediate surgical intervention was not offered and he was asked to be reviewed later.

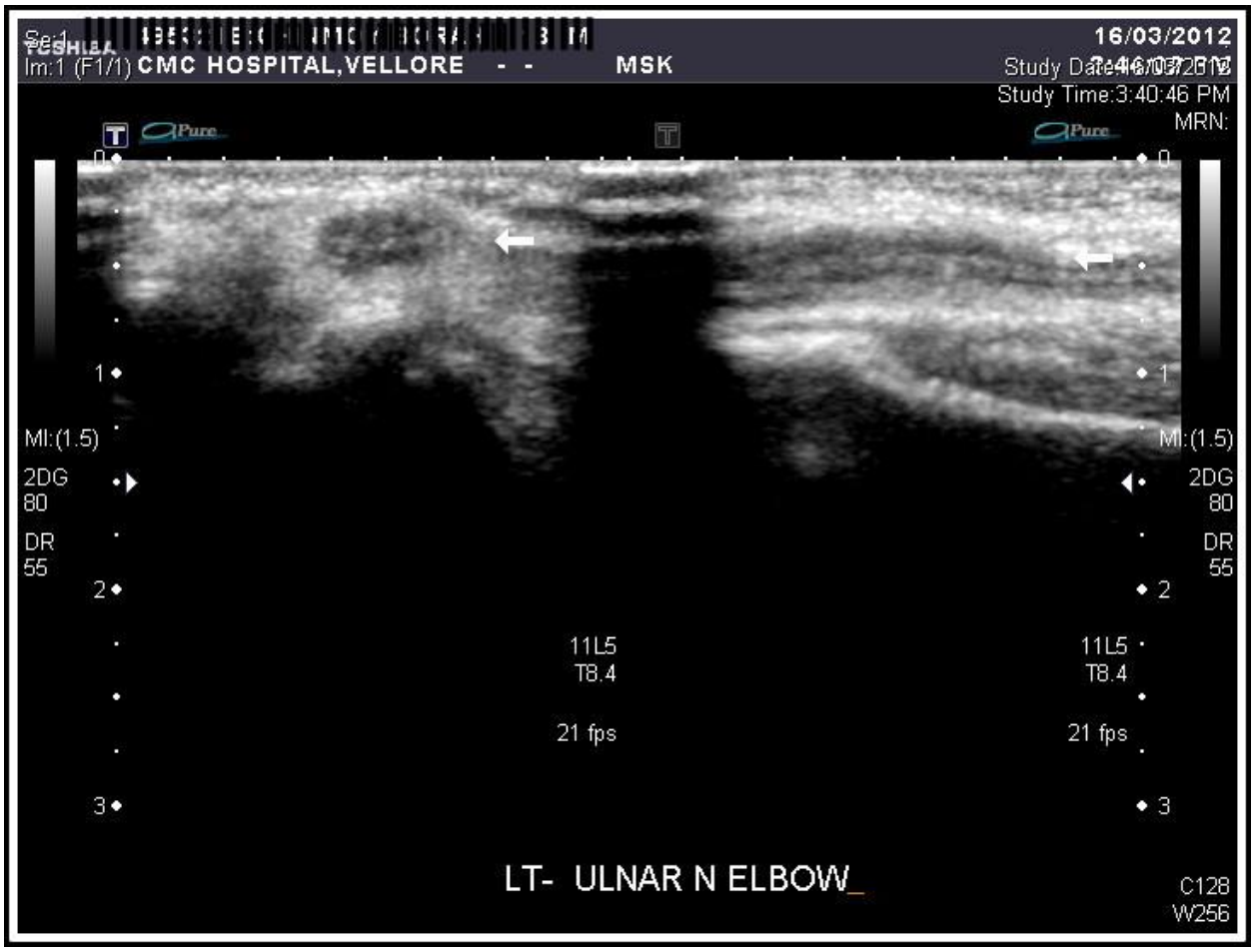


Fig 6.1: Ultrasound of Left elbow and ulnar nerve showing swollen ulnar nerve section proximal to retrocondylar groove.

A 42 year old shopkeeper, had signs of severe ulnar and median neuropathy with wasting of thenar and hypothenar muscles in his right hand, with symptoms of UNE in his left hand (Figure 6.2 and 6.3). The main complaint which had brought him was repeated haemoptysis for which he was evaluated and tuberculosis was ruled out. He had recurrent bleeds in bilateral elbow joint between the ages of 15 to 20 years which were not treated properly following which he developed clawing of right hand. However on examination he was found to have tight, shiny and stretched skin over the extremities, severe median and ulnar neuropathy in his right hand and U.N.E was found clinically and by NCS on left side. He was

referred to the department of Dermatology for further evaluation of the condition but was lost to follow up. His skin smears for AFB was negative.

Fig 6.2: Severe ulnar and median neuropathy in a patient with haemophilia with wasting of hypothenar muscle and FDI muscle wasting.

Fig 6.3: Severe UNE in the left upper limb and severe ulnar and median neuropathy with clawing in the right upper limb and impaired ability to place left hand in “intrinsic plus” position..

Limitations of the study:

The people with haemophilia, who are faced with serious musculoskeletal and other acute hemorrhage related complications, do not pay attention to a slow progressing and intermittently symptomatic condition like U.N.E. The haemophilia patients and their caregivers, who were seeking treatment in CMC Vellore, were unaware of U.N.E. The people with symptoms also thought it is a normal transient phenomenon, while many of them sought treatment for more serious problems which asked for immediate attention. The study population cannot be said to represent the haemophilic population in the community.

The technique of inching or including a third stimulation point at the elbow between above elbow and below elbow points has been described in many studies done on non haemophilic patients with U.N.E for exact localization of the nerve compression (91,92). In our study we could not do the same as the tissue around the elbow in many joints was swollen had lost their anatomical land marks and more points of stimulation around the joint with hypertrophied synovitis could increase the risk of bleeding. It was not needed as we did electrophysiological studies to screen for the condition rather than finding out the exact site of localization.

The inability to do needle EMG in cases where diagnosis of UNE was ambiguous, due to risk of bleeding, was not a major setback as all the cases of U.N.E and their findings could be corroborated with clinical signs and NCS.

CONCLUSION:

- The prevalence of UNE in people with haemophilia attending CMC, Vellore, a tertiary care hospital in South India was found to be 42/100 haemophilia population.
- The most common symptom among patients who had UNE was vague pain experienced in medial aspect of elbow and/or in the ulnar border of the hand. The most common sensory sign was impaired sensation to pressure with a 10 gram monofilament (9%). The most common sign of motor impairment was wasting in FDI (17%). The NCS data also showed demyelination and axonopathy changes more in FDI (24%).
- The study shows that the prevalence of U.N.E is much more than what is generally presumed in the haemophilia patients. The frequent bleeds in the elbow joint predispose to development of U.N.E.
- An association between the increased frequency of joint bleeds (> 3 bleeds in last 6 months) and U.N.E was found with a relative risk of 3.69.
- No association was found between stage of haemophilic arthropathy and U.N.E and this finding was statistically significant.
- The positive association was found between medial joint involvement or ulno humeral joint involvement and U.N.E and it was statistically significant (Odds ratio -1.36 and p – value 0.0212).
- The presence of habits putting the elbow at risk namely leaning over the elbows (Odds ratio of 1.4) or sleeping with elbows fully flexed (Odds ratio of 4.4) or both (Odds ratio of 3.3) were found to be associated with increased risk of U.N.E and the finding was not found to be statistically significant (p value = 0.05).

Scope for further studies and recommendations:

- The detection of U.N.E by electrophysiology without using an inching technique has the disadvantage of inability to localize the lesion. Use of Ultrasonography as a screening tool along with NCS can help in increasing the specificity and sensitivity of the test and in localizing the exact site of ulnar nerve compression. This will aid in planning the surgical management of U.N.E.
- To ascertain, if U.N.E is the cause of poor writing speed and endurance in children with haemophilic elbow arthropathy, studies can be designed where hand functions of those diagnosed with U.N.E can be checked by objective methods like use of JAMAR device or using the pinchometer.
- It is essential to educate patients and caregivers about U.N.E and prevent recurrent elbow bleeds as it has been found to be associated with increased risk of developing U.N.E. In patients where the elbow is a target joint, screening for U.N.E as a routine practice should be practised even when the patient doesn't complain of any symptoms.
- Education about avoiding the habits which put the ulnar nerves at risk of compression is important in all patients with haemophilia.
- It is possible for a child to have U.N.E even in absence of active joint bleeding in the elbow joint. During examination, the patients who are detected to have U.N.E must be given the options of giving their examinations orally or using a writer, even in the absence of an active bleed as the inability to write fast or legibly can have their academic implications.

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